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BRAIN NETWORKS IN TIME: DERIVING AND QUANTIFYING DYNAMIC FUNCTIONAL CONNECTIVITY

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Brain Networks in Time: Deriving and quantifying dynamic functional connectivity

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Abstract

Studying the brain's structure and function as a network has provided insight about the brain's activity in health and disease. Networks in the brain are often averaged over trials, frequency and time and this is called functional connectivity. This thesis aims to extend the analyses beyond these assumptions and simplifications. Connectivity that varies over time has been called dynamic functional connectivity. This thesis considers different ways to derive a dynamic functional connectivity representation of the brain and subsequently quantify this using temporal network theory.

Paper I: discusses different interpretations about what can be considered "interesting" or "high" dynamic functional connectivity. The choices made here can prioritize different edges.

Paper II: discusses how the stability of the variance of dynamic connectivity time series can be achieved. This is an important preprocessing step in dynamic functional connectivity as it can bias the subsequent analysis if done incorrectly.

Paper III: quantifies the degree of burstiness, the distribution of temporal connections, between different edges in fMRI data.

Paper IV: provides an introduction and application of metrics from temporal network theory onto fMRI activity.

Paper V: multi-layer network analysis of resting state networks over different frequencies of the BOLD response. This work shows that a full analysis of the network structure of the brain in fMRI may require considering networks over frequency.

Paper VI: Investigates whether the functional connectivity at time of trauma for patient with traumatic brain injury (TBI) correlates with features related to long term cognitive outcome.

Paper VII: is a mass meta-analysis using Neurosynth to cluster different brain

networks from different tasks into a hierarchical network structure. This provides the start of a data driven hierarchical network atlas for different tasks.

Paper VIII: is a conceptual overview of the different assumptions made in many popular methods to compute dynamic functional connectivity.

Paper IX: aims to evaluate different dynamic functional connectivity methods based on several simulations designed to track a signal covariance that fluctuates over time.

List of scientific papers

I **Thompson, W. H.**, & Fransson, P. (2015). The mean–variance relationship reveals two possible strategies for dynamic brain connectivity analysis in fMRI. *Frontiers in Human Neuroscience*, 9(398), 1–7.

II **Thompson, W. H.**, & Fransson, P. (2016). On Stabilizing the Variance of Dynamic Functional Brain Connectivity Time Series. *Brain Connectivity*, 6(10), 735–746.

III **Thompson, W. H.**, & Fransson, P. (2016). Bursty properties revealed in large-scale brain networks with a point-based method for dynamic functional connectivity. *Scientific Reports*, 6, 39156.

IV **Thompson, W. H.**, Brantefors, P., & Fransson, P. (2017). From static to temporal network theory – applications to functional brain connectivity. *Network Neruoscience*, 1(2), 1–37.

V **Thompson, W. H.**, & Fransson, P. (2015). The frequency dimension of fMRI dynamic connectivity: network connectivity, functional hubs and integration in the resting brain. *NeuroImage*, 121, 227–242.

VI **Thompson, W. H.**, Thelin, E. P., Lilja, A., Bellander, B. M., & Fransson, P. (2015). Functional resting-state fMRI connectivity correlates with serum levels of the S100B protein in the acute phase of traumatic brain injury. *NeuroImage: Clinical*, 12, 1004–1012.

VII **Thompson, W. H.**, & Fransson, P. (2017). Spatial confluence of psychological and anatomical network constructs in the human brain revealed by a mass meta-analysis of fMRI activation. *Scientific Reports*, 7, 44259.

VIII **Thompson, W.H.**, & Fransson, P. (*Manuscript*) A unified framework for dynamic functional connectivity.

IX **Thompson, W.H.**, Richter, C., Plavén-Sigray, P. & Fransson, P. (*Manuscript*) A comparison of different dynamic functional connectivity methods.

List of additional scientific papers which are not included in the thesis

I Richter, C. G., **Thompson, W. H.**, Bosman, C. A., & Fries, P. (2015). A jackknife approach to quantifying single-trial correlation between covariance-based metrics undefined on a single-trial basis. *NeuroImage*, 114, 57–70.

II Richter,* C. G., **Thompson,* W. H.**, Bosman, C. A., & Fries, P. (2017). Top-Down Beta Enhances Bottom-Up Gamma. *Journal of Neuroscience*, 37(28), 6698–6711. * Authors contributed equally

III Plavén-sigray,* P., Matheson,* G. J., Schiffler,* B. C., & **Thompson, W. H.** (2017). The readability of scientific texts is decreasing over time. *eLife*. Accepted. * Authors contributed equally

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Abbreviations

AAL	Automated Anatomical Labelling
ADHD	Attention Deficit Hyperactivity Disorder
ANL	Automated Network Labelling
BOLD	Blood Oxygen Level Dependent
CNS	Central Nervous System
DFC	Dynamic Functional Connectivity
GOS	Glasgow Outcome Scale
ECoG	Electrocorticography
EEG	Electroencephalography
FC	Functional Connectivity
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy
HCP	Human Connectome Project
HMM	Hidden Markov Model
HRF	Haemodynamic Response Function
ICA	Independent Component Analysis
MEG	Magnetoencephalography
MRI	Magnetic Resonance Imaging
PCA	Principle Components Analysis
PET	Positron Emission Tomography
SCA	Seed Correlation Analysis
SPM	Statistical Parametric Mapping
TBI	Traumatic Brain Injury
TR	Time Resolution

Chapter 1

A temporal network model of the brain

1.1 Introduction

This thesis is about creating a model to quantify brain activity. The model assumes two key attributes (1) the brain is structured as a network and cognitive processes occur within that network (2) a dynamic perspective is needed in order to understand the function of cognitive processes.

Part 1 is an introduction to the papers in the thesis is and it is divided into four chapters. Chapter 1, will elaborate upon the reasoning behind creating a model for quantifying brain activity. Thereafter, motivate the two key attributes of networks and time. Chapter 2 will give an overview of the research areas of functional connectivity, dynamic functional connectivity, network theory, and temporal network theory. It further discusses some of the issues and problems that exists within these fields. Chapter 3 discusses each of the works contained within this thesis, connecting them to the overall goal of creating this dynamic network model of the brain, and discusses some future directions. Chapter 4 describes the availability of both the code and the data used in the words in the thesis. Part 2 of this thesis is the nine attached papers.

1.2 A model of the brain

There is something fascinating about cognition. It can decide, anticipate, plan, feel, remember, give the appearance of free will, and generate conscious. The same input can lead to several different outputs due to different cognitive faculties are used. Within seconds thoughts can dwell on autobiographical memories from childhood, switch to a high motor skill task like drawing, and then participate in a political debate. In short, to understand how we function this flexibility needs to be understood.

To move towards increasing our understanding of our cognitive repertoire and its flexibility, there are multiple ways one can go about it. Some have tried to isolate some faculty which is unique to our species, but this endeavour appears to fail to identify any category or property of cognition which is unique—even very niched properties, such as recursive understanding, has met critique. Others want to reduce the cognitive properties as a product of some first principle, which is often problematic due to scope and scale of brain function.

An alternative approach is to create a model. A scientific model can be more complex than relying on a first principle, it not need to make strong claims about the models uniqueness, and is more flexible to revise when new evidence is presented. The model's utility is to assist understanding and make testable predictions. Models can also be contrasted with other models to see the scope of their fit and the simplicity of their construction.

What is the point of the model? It frames the perspective about what is being investigated. When viewing a problem from a certain direction, it will lead to natural next steps to head towards. This thesis aims to build towards a model. This entails that, given some data of the brain, we can quantify and analyse this data in a certain way. Given a good model, this will then expand upon our current knowledge of the brain and give testable predictions going forward. Specifically in this case, the model should allow us to investigate, quantify, and expand our knowledge regarding the flexibility of cognition.

In this subsection, the type of model that this thesis is working towards is

stated. In §1.2 and §1.3 the two main assumptions of the model will be motivated. To do this, I begin by outlining simpler, but insufficient models, of how we think cognition may work. *Figure 1.1* depicts the models that are discussed below. Some overall starting point is needed: one assumption in all models is that cognition always involves an agent that receives input from it environment and acts within it.

Model 1 in *Figure 1.1* depicts a reactionary agent. Some agent which have been described to have this type of circuitry (e.g. ticks were described this way by von Uexküll (1)). Based on the input of from receptors, the action taken is necessary. This leads to a simple cause–effect model of a agent acting in its environment. Here there may be a repertoire of actions based on a repertoire of inputs. Von Uexküll described the ticks behaviour as consisting of three different receptor-effector cycles where the tick could jump after detecting an odour, move based on temperature and find a place to bite based on touch (1). This is obviously an insufficient model to describe cognition as it fails to account for any processes which occur within the agent.

More complex agents are considered to have additional processes that occur when receiving input from the world. This is what Model 2 shows in *Figure 1.1.* These additional processes could be memories, anticipation, contextual information, instructions etc. This seems to be the hallmark of cognitive processes, the simple cause–effect chain is broken by additional processes within the subject. This does not necessarily mean that a type of "free will" is needed just that processes are evaluated with more complex processes than acting only on the receptor information. The internal processes seem to add additional layers of complexity to the relationship between the agent and the environment (e.g. using tools). For any cause, there appears to be a repertoire of possibilities that the internal system considers. When changing the internal system (e.g. via arousal) different decisions are taken. New tasks can also be learned, adapting to new information. This second model only says that these processes exist. It has very little consideration regarding their limitations and how they are instantiated.

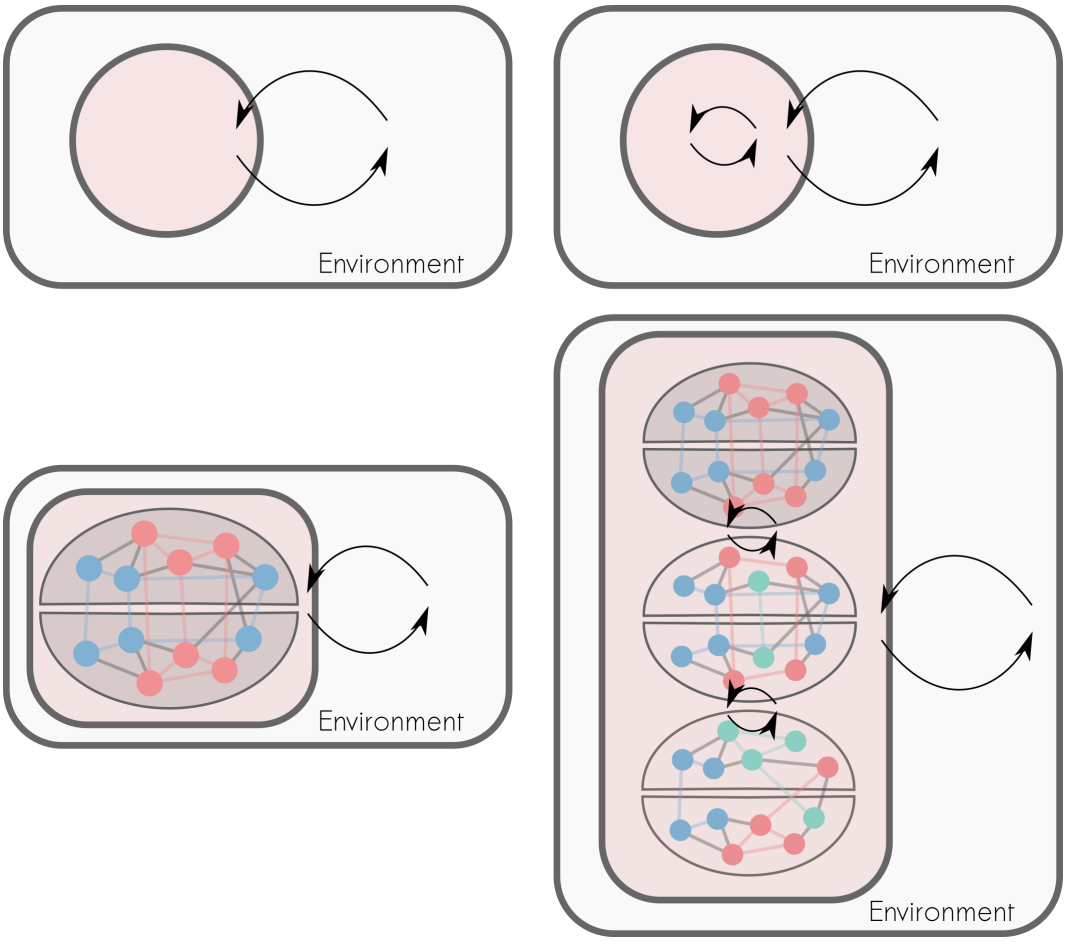

Figure 1.1: An illustration of different types of models of cognition regarding an agent's relationship with its environment. Top-left: Model 1. A reactionary agent gets input from the environment and this leads to an output. Top-right: Model 2. This is the same as the previous model but now includes additional processes that occur within the agent. This may be processes like memory or anticipation that modulate the input or output. Bottom-left: Model 3. This is the same as Model 2 but now includes some structure for how the processes within the agent occur. Bottom-right: Model 4. This is the same as Model 3 but now includes that the structure of the internal model changes. In this figure one of the three possible structures is chosen.

A third model is to map or model the processes within the agent. All the different cognitive processes to different areas or different networks in the brain. This places restrictions on how the different cognitive processes can occur. There are many models that could fit this criteria. *Figure 1.1* depicts a network based model. There are many other forms that Model 3 can take (the network model is motivated in §1.2). This will map brain processes and infer cognitive processes (i.e. when brain areas A, B and C are active, then the agent is doing process X). This appears to be a popular model with how many consider mapping cognitive processes in neuroimaging today. The benefits of these type of models is that they can detail how different cognitive processes are instantiated. A downside of this type of model is that, while accounting for slow changes when learning, these models often fail to consider the flexibility within the system.

A fourth model argues that the internal processes that occur are more flexible than in Model 3. This entails that the internal system is more fluid and can take different configurations. This fluidity does not entail an "anything goes" scenario where any configuration is possible. A large part of this model will be to find the limits of the flexibility. The system reconfigures which entails the same input can get treated very differently based on different reconfiguration of the system. The internal configuration of the system can also change during the processing of an input. In practice, this model entails that the distributed patterns will be constantly changing in time. This means that isolating a cognitive faculty does not occur like Model 3 (i.e. "activation of this subset of distributed brain areas") but instead allows for sequences of different configurations to occur during the performance of some cognitive faculty. It also means that certain internal configurations may be harder to achieve, given a specific state of the system.

It is the fourth model which this thesis builds towards and justify. The motivations behind the need for both the distributed processes and time are included in §1.2 and §1.3.

Note that a dynamic distributed model of the brain is not unique for this thesis.

Many others postulate a similar model of distributed dynamics (see §1.4). The difference with the works in this thesis is that the aim is to appropriately quantify a network perspective and make it a dynamic perspective. This choice is partially motivated by the neuroimaging modality that is used.

1.2.1 Neuroimaging choices

The model that is created in this thesis is based on neuroimaging results from functional magnetic resonance imaging (fMRI). Why is this? There are two clear downsides to using fMRI. First, the blood oxygen level dependent (BOLD) contrast is measured in fMRI, it is an indirect measure of neural activity. Second, the sampling frequency of fMRI ranges between 2 and 0.4 samples per second. fMRI is very slow when contrasted to magnetoencephalography (MEG), with a sampling rate of 1000 per second. There are however benefits using fMRI. There is a greater spatial resolution than other non-invasive imaging. The distributed network patterns were first identified in fMRI and the methods to derive the networks are more established.

While possible to use MEG for its higher temporal resolution, it has a worse spatial resolution and not all parts of brain networks are always identified in studies. There is also an additional complication of cross-frequency interactions which would have to be accounted for. This makes the representations needed in MEG more complex than those discussed in this thesis. It is a natural progression to go with the simpler network-time models for fMRI and extend to network-time-frequency models than vice versa. Other imaging alternatives such as the invasive electrocorticography (ECoG) generally have partial coverage of the brain.

This means that there is generally a heavy bias towards fMRI research in this thesis. While methods to derive dynamic connectivity in MEG become slightly different due to different frequency information also playing a critical role and different types of artefacts that need to be dealt with, temporal network theory can still be applied.

In sum, this thesis discusses two main parts: creating a dynamic network representation and quantifying that representation. The first part is optimized for fMRI research. The second should be generalisable across imaging modalities, given an appropriate dynamic network representation.

1.3 Distributed processes in the brain

The history of neuroscience has emphasized the importance of neurons and their synaptic connections. Early work on distributed processes in the brain saw multiple disciplines embrace the idea that the brain used multiple units for processing. Hebb (1949) in *The The Organization of Behavior* (2) wrote about the importance of connections strengthening when neurons became active. Ashby's (1952) work in cybernetics discussed how the brain will need multiple coordinating parts reaching temporary stabilities to coordinate with the environment through time (3). The first wave of artificial neural network research where collections of processing units (perceptron) were created (4,5). For various reasons, both dominant theories in psychology, cognitive science and artificial intelligence strayed away from such 1960 through to the 1980s where modular compartment and symbolic processes were the dominant ideologies. In the latter half of the 1980s and beginning of the 1990s when whole brain brain mapping of connections started to reach importance with studies in C. elegans (6), non-human primates (7–9) and the second wave of neural network research (connectionism) (10).

The idea of different brain areas being structured to segregate and integrate information started to mature in the 2000's and these ideas became known under the name of "connectomics" (11,12). Mapping the human connectome has become an established paradigm in cognitive neuroscience. It is well established that there is a sensory hierarchy in visual perception, with receptive fields growing larger as additional features are integrated through time (see (13) for discussion about sensory and motor hierarchies). Decoding of semantic maps, for example, revealed larger distributed areas of cortex are involved

(14). The rise of connectomic focused research means that it is now common to hear "<cognitive function> network" instead of "<cognitive function> brain area" which was more dominant prior to connectomics (although it is also heard today by some researchers).

Distributed representations in the brain can be applied to multiple scales and imaging modalities of the brain. The multiple scales are often vaguely defined as microscale (e.g. micro circuits of several neurons), macro level (e.g. voxels containing many tens of thousands of neurons) or an interlinking scale (mesoscale). This thesis is generally focusing on the macro scale. Connectivity is known to be partly determined by genetics, (15) and that they differ enough between people to infer a "fingerprint" across tasks (16). Despite this, there are distributed network patterns are known to exist during tasks and are thought to play a role in cognition (17,18). Thus any model of cognition should be assuming a distributed network pattern where the processes occur. This justifies both Model 3 and 4 in §1.2.

1.4 A dynamic perspective of the brain

A lot of research on distributed patterns in the brain has focused on anatomic studies or studies that average over time or trials. The brain does not structurally reconfigure when performing a new task. However there is an increasing amount of studies regarding the neural activity on the anatomical networks changes through time. This entails that activity can be modelled on networks on multiple time scales (18). When starting to consider that the activity of the brain networks has some flexibility or can instantiate with multiple configurations, then Model 4 of §1.2 is being considered. If instead, the configurations of functional connectivity is assumed to be stable, Model 3 is being considered.

The brain is a dynamic organ. The activity in the brain changes based on new inputs and on the internal state of the brain. Thus, a good model of the brain will consider how existing processes reconfigure into new processes. This requires treating the brain as a system with its own state space that might act

differently under different circumstances. A fluctuating internal state space of a system can then act flexibly with the environment. If the features of the state space are connections in a network, then the fluctuating state space entails that the configuration of network is changing.

By using the word *dynamic*, it implies that some change is involved. Change must occur over some period of time. The temporal scale depends on the object of study. For an engineer building a machine with multiple coordinated parts, being a few milliseconds off could be disaster, whereas for a geologist, the smallest time unit considered for some processes will be millions of years.

When considering the brain as a dynamic organ there are multiple time scales that can be considered as there is by necessity no predefined temporal scale that the model must adhere to. The time scale is also dependent upon what spatial scale is being considered. It can take only a few milliseconds for ion channels to return to baseline (19) whereas developmental processes play out over years. To get a complete understanding of how the brain works, we will need an understanding of brain function in evolutionary, generational, developmental/ageing time scales.

With non-invasive neuroimaging, the smallest time scale that can be achieved is in seconds (for fMRI) and milliseconds (for EEG and MEG). Thus, the chosen imaging modality sets limits on the time-scales for which we can study cognitive processes on. The focus throughout this thesis has been on these time scales, by trying to isolate cognitive processes through interactions of large scale brain network systems. This allows us to study characteristics of imaging data that potentially reflect the temporal scale for which different cognitive processes interact and transition. The exception to this general time scale is *Paper VI* which deals with a time scale of several months.

Regarding dynamic properties and the brain, there has been considerable amount of research with different ideas to underlying temporal properties and mechanisms. A lot of studies have addressed how neurons or neuronal circuits communicate so that they can dynamically coordinate their information (20–23). This often involves some mechanism of coordination. Coherence has

been postulated as such a mechanism (21). Criticality is another property that dynamic systems have explored, where there is a scale free distribution of transitions within the state space of the system (24,25). Metastability is another property which has received a fair amount of attention (20,26–28). Here a dynamic system reaches a point of local stability in the system and remains there for some time (often until more energy is added). It is a property which has been postulated to exist over multiple spatial scales, from single neurons to electrophysiological recordings (28). Interestingly, metastability and coherence have been considered to be complementary (29). Changes in metastability has also been inferred when structural connectivity is damaged (30). These dynamic properties give us some indication about how we expect network patterns to act, but many of these studies do not consider network representations of the brain. As stated in §1.3, it is now well established that neuronal activity on networks changes through time (both on a longer time scale through learning and shorter time scales such as performing a task (18)). Recent evidence has however shown that different areas of the cortex may function on different time scales (ranging from 200-1000 milliseconds to seconds) (31).

1.5 Summary of Chapter 1

This thesis is about establishing an appropriate way to derive and quantify dynamic networks. In doing so, cognition is being modelled as Model 4 instead of Model 3 outlined in §1.2. While this turn to dynamic network patterns is far from unique in this thesis, what this thesis tries to establish is the correct way in deriving this distributed representations in fMRI and then an appropriate way to quantify these representations. As will be shown in §3.5, many works today postulate dynamic properties may not be doing so. Further, if representation are poorly derived, the model has little value. The next chapter discusses the literature and problems of deriving and quantifying these dynamic distributed models of cognition.

Chapter 2

Literature overview

2.1 Introduction

This section provides on an overview of four different areas of research that aim to create and quantify a distributed representation and/or a temporal representation. Given the assumptions from §1.2-§1.4, a dynamic and distributed model to quantify cognitive processes is assumed to be needed, we begin by first discussing how to create a distributed model and then how to extend the distributed model to a distributed and dynamic model. The reason for this order is due to the large body of work investigating static networks with fMRI.

Starting with a static network approach, there are two important issues:

1. How to derive a representation of the distributed patterns of activity or network.
2. What is an appropriate way to quantify the properties of the representation.

Regarding issue (1) the distributed representation are commonly quantified by calculating the degree of connectivity. This is done by quantifying the relationship between different brain areas. Regarding a connectivity based

representation, there are three ways in which this representation can be constructed:

> *Structural connectivity*: characterizing the anatomical or structural pathways in the brain through various tracing or tractography methods (e.g. Diffusion Tensor MRI).
>
> *Functional connectivity*: characterizing the relationship between two or more areas of the brain where the relationship is inferred from measuring and correlating activity from the brain.
>
> *Effective connectivity*: characterizing the causal relationship between two or more areas of the brain where the relationship is inferred from measuring and quantifying activity from the brain.[1]

The activity measured from the brain is restrained by the underlying anatomical structure, but it is not the focus in this thesis.[2] In the human brain, connectivity patterns between brain regions were first identified with between-subject correlations in PET (38).[3] The use of functional connectivity in fMRI

[1]Effective connectivity suffers from the difficulty of estimating causal relationships. In neuroimaging, three of the most common approaches are transfer entropy (32), Granger causality (33–35), and dynamic causal modelling (36). Many causality algorithms suffer from the possibility of a unknown source causing the behaviour of both, although there are claims that dynamic causal modelling can account for this (37), it requires additional assumptions in the model. There has been little focus on attempting to characterize effective connectivity in this thesis due to the difficulties effective connectivity has with fMRI.

[2]The focus of this thesis is functional connectivity. Structural connectivity is important to allow for the possibility of functional connectivity, but structural connectivity does not necessitate high functional connectivity. Instead, its indicates a potential for functional connectivity. To draw an example, train lines may combine three cities: A, B, and C. The different cities have different number of trains travelling along the tracks. The train lines are analogous to the structural connectivity as they constitute a physical connection. The number of trains travelling between the stations are analogous to functional connectivity. With this example we see how the functional connectivity is restrained by the anatomic connectivity but illustrates how it functions somewhat independently of it. Thus, although functional connectivity is restricted by structural connectivity, it receives little attention in this thesis. This simplification entails that the model of the brain that is being created in this thesis could be improved on by adding this information.

[3]Here correlations were obtained by correlating over subjects, not over the within-subject neuroimaging time series, which is typical for most functional connectivity studies today.

exploded in popularity after Biswal et al in 1995 (39) founda correlation between left and right motor cortex during a recording session when no task was present within single subjects. This started a wave of research over the last two decades where researchers have studied functional connectivity in fMRI. An alternative approach to functional connectivity is to derive a collection of patterns of activity from different areas of the brain associated with an event, instead of interring a relationship between the different areas of the brain (see §2.2.5).

Once this representation of different brain areas has been derived, issue (2) quantifying the representation, can be addressed. The different types of connectivity forms a representation with clusters of correlated brain areas, allowing for different *brain networks* to be identified.[4] It can be as a network object to quantify different properties using network theory. Network theory can be defined as:

> *Network theory*: a way to model and quantify distributed representations.

A functional connectivity representation is a network. With this representation, the configuration and properties of the network can be analysed. For example, some areas in a network may connect to many different areas (sometimes called hubs). Different types of properties that can be derived using network theory are discussed in §2.4.

[4]There is slightly overlapping and potentially confusing terminology used within cognitive/systems neuroscience. *Network theory* is a way to model and analyse the relationships of connected areas. Network theory uses a mathematical object called a graph to denote the distributed representation. This mathematical object, within network theory, is referred to as a network (see §2.4). However, within cognitive neuroscience, the term *network* also refers to distributed areas of the brain that are functionally associated with some task or show larger degree of connectivity compared to other brain areas. In network theory, these are technically a module, a subnetwork, or a cluster within the entire distributed representation (i.e. the network). Whenever the term "brain network" or "networks of the brain" is used, it refers to a these modular components of the network (i.e. network within cognitive neuroscience). Whenever network is used in isolation, it refers to the graph object (i.e. network within network theory).

Dynamic functional connectivity is an extension of functional connectivity. Many of the works in this thesis consider the appropriate ways to derive and analyse this. In broad terms dynamic functional connectivity can be derived as:

> *Dynamic functional connectivity*: characterizing ongoing fluctuations or changes of distributed representations.

This creates a different type of representation compared to functional connectivity as the quantified relationship is extended through time. A schematic difference between the representations dynamic functional connectivity and functional connectivity is illustrated in *Figure 2.1*.

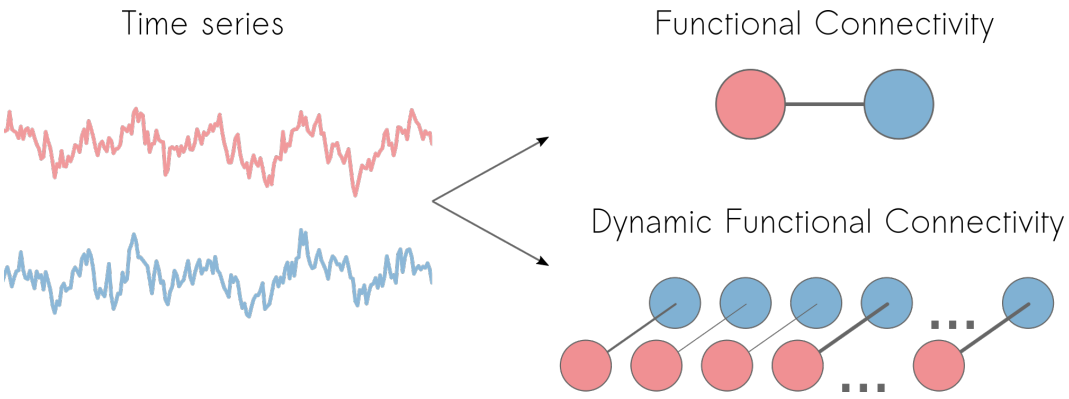

Figure 2.1: Schematic of the differences between functional connectivity and dynamic connectivity. The time series from two regions of the brain (left) gets transformed into a single representation of their connection in functional connectivity (top-right). In dynamic functional connectivity the connections between the two regions vary over time (bottom-right).

Just as network theory can quantify a functional connectivity representation, there are different methods to quantify the dynamic functional connectivity representation. Some of the methods include:

> *Variance of dynamic connections*: quantifying the variance of each connection of the dynamic functional connectivity representation.

> *Clustering of time points*: sorting the different connectivity representations over time into a discrete number of clusters or states.

Temporal network theory: a way to model and quantify dynamic or fluctuating network representations.

The majority of current studies published using a dynamic functional connectivity representations use the first two methods. These can be problematic for several reasons (see §3.2.6).

Temporal network theory can be applied to many methods of dynamic functional connectivity. Temporal network theory can also be applied to situations where functional connectivity is repeated at different time points (e.g. once per year). Thus, while well suited to study dynamic functional connectivity, temporal network theory is not exclusive to dynamic functional connectivity (See §1).

This chapter continues with a more in depth discussion of different aspects of functional connectivity, dynamic functional connectivity, network theory, and temporal network theory. Each one of these four properties will be explained in greater detail, stating what is known within each. This chapter concludes with an overview of software that exists to quantify these different concepts.

2.2 Functional connectivity

2.2.1 The fundamental assumption of functional connectivity

The fundamental assumption behind functional connectivity is that when brain areas show a correlation in brain activity, there is communication between those areas. There are different ways to calculate this correlation, but the assumption remains the same.

There is some support for this assumption. There is a relationship between structural and functional connectivity (40–42). It is also possible to identify similar network patterns in multiple imaging modalities apart from fMRI, in-

cluding MEG (43–47) and ECoG (48) which are both direct measures of neural activity in contrast to the BOLD signal in fMRI. There is some evidence against this fundamental assumption. First, that correlations can be driven by an external noise factor such as motion (49–52). Second, that the correlations can still occur between temporal poles in the brain after surgically removing the connections (53).

The assumption stated above uses the word "communication" vaguely. For example, if three brain areas are correlated in their activity (A, B, and C), different underlying communication pathways are possible, especially when the temporal resolution is low or the signal is sluggish like in fMRI. For example: A communicates with B, and B communicates with C. Alternatively, all three areas could be communicating with each other. This cannot be disassociated in most functional connectivity measures. Thus considering the "communication" inferred from the fundamental assumption, there are two possible interpretations regarding the nature of the communication:

> *Strong communication*: There is a direct link between two brain regions when they exhibit high functional connectivity.

> *Weak communication*: There is similar or shared information between two brain regions when they exhibit high functional connectivity. This connection can be indirect.

The difference between weak and strong communication is illustrated in *Figure 2.2* where three different areas are connected with a binary connection. The weaker assumption allows for considerably different underlying activity processes to occur in the network. The weak communication assumption is the safer option and, aside from the signal being due to non-neuronal sources, it answers the criticisms directed towards functional connectivity. However, there are some arguments that offer support for the strong communication assumption. By tracing the anatomical projections in Macaque monkeys, it was shown that networks are more dense (i.e. more connections present) than pre-

viously assumed (54). The weak assumption is considered the most plausible in this thesis.

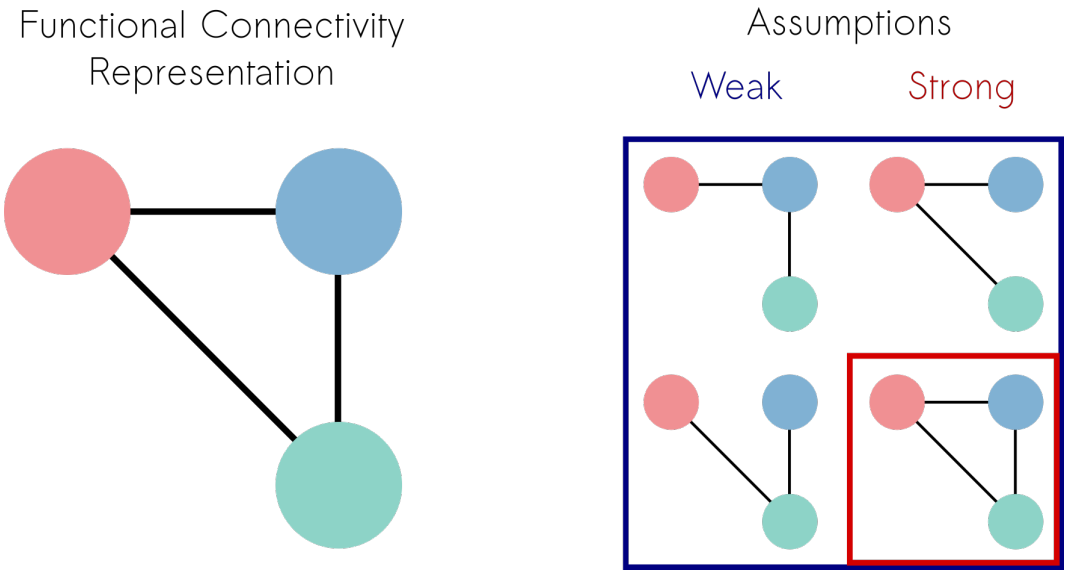

Figure 2.2: Illustrating the differences between strong and weak communication. Three regions are connected through functional connectivity estimation (left). There are four different possible configurations given the weak communication assumption (right, blue). The strong communication assumption only allows the fully connected representation (right, red).

The weak communication assumption is similar, for all intents and purposes, to the assumptions needed for conducting brain activity pattern analysis. In multivariate pattern analysis (see §2.2.5), collections of regions or voxels are quantified as being involved in a given process. In sum, the weak communication assumption of functional connectivity is reasonable. The weak communication assumption will be important when deriving and interpreting dynamic functional connectivity.

2.2.2 Deriving functional connectivity

Functional connectivity was shown to be present during periods without any task (39). This became known as "resting-state". A recording session where the subject "rests" (i.e. either watches a fixation cross or has their eyes closed) usually lasts between 5-10 minutes. The most common way to derive functional

connectivity is to perform at correlation between the time series' of two brain regions, usually using the Pearson correlation coefficient or using a general linear model. This can be done with a specific region of interest in the brain (sometimes called Seed-based Correlation Analysis (SCA)) or by reducing the voxel information to a parcellation of brain regions. There are however other measures to derive connectivity. Independent Component analysis (ICA) is common technique (17,55,56) which finds a designated number of components which consist of spatial patterns that behave in a similar way. Additional methods used to quantify functional connectivity are regional homogeneity (ReHo, (57)). Certain methods uses frequency information where one of the most popular is the "amplitude of low frequency fluctuations" (ALFF,(58)). Additional studies deriving connectivity using the frequency information have used wavelets to derive mutual information (59), coherence (60), and the power spectral density (*Paper V*). Additional frequency measures such as phase synchronization have also been used (61).

2.2.3 Functional connectivity and neuronal activity

The BOLD signal that underlies the derivation of functional connectivity in fMRI is a indirect measure of neuronal activity. The BOLD has been shown to reflect neuronal activity (62) but it is critical that functional connectivity also relates to neuronal activity and not some common source of noise.

Simulations have shown that functional connectivity in the BOLD signal is a result of oscillatory brain activity (63). As previously mentioned, MEG, which directly measures neuronal activity, have identified similar resting state networks (43–47,64). Later work has identified that different frequencies from MEG connectivity results are connected to different connections in fMRI (65). This evidence from multi-modal and multi-frequency analysis strongly suggest that brain dynamics needs to viewed from a spectral-spatio-temporal perspective of neuronal activity (66).

Non-neuronal signal sources are however a problem for functional connectiv-

ity analyses in fMRI. This include noise from physiological sources such as heartbeats and breathing, but these are generally found in frequencies higher that 0.1 Hz (67). Micro head-movement is a known source of noise (49–51) which has lead for the need to "scrub" the data for artefacts related to micro-movement. Further, movement artefacts effect the BOLD signal differently over the frequency range 0.007-0.167 Hz (68).

2.2.4 Applications of functional connectivity

The range of applicability of functional connectivity obtained from neuroimaging experiments is vast, and it keeps increasing over time. Applications of functional connectivity can be placed into three different categories (i) general activity during rest; (ii) explaining of cognitive/psychological processes; and (iii) studies of differences of brain connectivity in healthy versus patient cohorts.

First, the application of functional connectivity has identified numerous properties regarding the brain's function. This includes the identification of brain networks both during rest and performing a task (17,39,55,69,70), identifying anti-correlations between the default mode network and task positive networks (71,72). Further, the effect of genes on functional brain connectivity has been examined (73). Regarding development, proto-networks have also been identified in new born infants (74,75).

Functional connectivity has been linked to many psychological properties and behavioural phenomena. The psychological concepts where functional connectivity has been identified include (but not excluded to): memory retrieval (76), working memory (69), cognitive load (77), selective attention (78), pain (79), imagination (80), emotion (81,82), cognitive control (83), anticipation (84), social cognition (85), and mind-wandering (86). Aside from being connected to psychological concepts, functional connectivity has also been directly related to behaviour. This includes: memory performance (87), reading ability (88), effect of meditation (89). Connectivity is also present during sleep (90), but

the long range connections break down (91).

Finally, functional connectivity has shown promise when applied to numerous diseases and disorders in the central nervous system (92,93). Differences that have been observed include: schizophrenia (94), depression (95,96), autism (97), Alzheimer's disease (98), social anxiety (99), traumatic brain injury (100,101), fibromyalgia (102,103), and obsessive compulsion disorder (104). There has long been a hope that functional connectivity may act as a possible biomarker for different diseases and disorders. However, it is argued later in §2.5.2, that since many differences between healthy controls and patient populations are found in similar networks, functional connectivity may not be sufficient in identifying disorders.

2.2.5 Pattern analysis

Aside from identifying functionally connected patterns, as mentioned above, it is possible to identify distributed patterns of brain activity but without deriving connectivity estimates. In these cases, no relations between the different elements of brain pattern activity are inferred. Instead, it finds patterns and classifies them using different techniques. As discussed above, this also requires a weak communication assumption as these patterns are seen to be doing something together. Pattern analysis techniques in brain imaging have had numerous successes in categorizing and decoding brain states (14,105–108). There is a subfield of research regarding the problem of identifying dynamic patterns of brain activity in electrophysiology (109), which is another way to approach Model 4 of §1.2. Many different approaches adopted from machine learning, both supervised and unsupervised machine learning, have been applied onto neuroimaging data, ranging from support vector machines (110–113) to deep learning algorithms (114,115). There is nothing necessarily antagonistic between the network and pattern approaches and they can even be integrated. Deep learning, for example, uses network architecture to model and make inferences about patterns (116).

2.3 Dynamic functional connectivity

Functional connectivity derives estimates of a relationship between two areas by correlating their activity over some period of time. Chang & Glover showed in fMRI that different regions of the brain during rest can fluctuate in their correlation (60). The aim of dynamic functional connectivity is to derive an estimate of fluctuations of connectivity that occur over time.

Generally, to derive a correlation estimate requires multiple observations. This leads to a problem for dynamic functional connectivity. It is desirable to robustly estimate the relationship between the two brain areas and be sensitive to changes in that relationship through time.

Some notes on terminology. Dynamic functional connectivity is sometimes referred to as time-varying connectivity in the literature. No difference between these two terms is made here. Further, when referring to the more traditional functional connectivity discussed in §2.2, the term "static functional connectivity" will be used.

2.3.1 Methods for dynamic functional connectivity

In the last five years, many methods have been proposed to derive dynamic functional connectivity from neuroimaging data. There are many ways these methods could be grouped, some are based on correlations, some use clustering methods, others assume that the connectivity estimate should use nearby temporal points, others assume that similar spatial configurations should be used. Here follows a quick summary of several popular methods.

Sliding window: a selection of adjacent time points are used to estimate the covariance relationship, most often with a Pearson correlation. The advantage of the sliding window method is that it is easy to understand and implement. The disadvantage is that there is a trade-off between being sensitive to noise and accuracy of the covariance estimate. See e.g. (117) or (118) for example

studies.

Tapered sliding window: same as the sliding window, except each collection of time-points are weighted according to a taper. The aim is to increase the temporal sensitivity with this method compared to the sliding window method as closer time points will receive a stronger weight (See e.g. (119) for an example).

Temporal derivative: by multiplying the derivative of the time series to track the fluctuating relationships between time series (120). The upside of this method is an increased sensitivity to non-stationarities, making it suitable for task-related data and it has higher temporal sensitivity compared to the sliding window method. The downside of the method is that, for stability, it still requires some temporal smoothing.

Jackknife correlation: Can be seen as a special version of the sliding window method. To estimate the time correlation at t, all time points but t are used. The result is then multiplied by -1. This gives a single time-point correlation estimate with optimal temporal sensitivity. Any noise that exists in the time series will be kept. This method is applied to estimating single trial Granger causality (121) and adopted for dynamic functional connectivity in *Paper IX*. See §3.2.3.2 for more details.

Point process: A collection of methods where time points are considered in isolation. They can get grouped together based on the properties of each time point ((122,123) and *Paper III*). Point process methods may be highly sensitive to noise. In some methods, only a portion of the data is used.

Hidden Markov Models (HMM): A unsupervised machine learning algorithm for time series which has been applied to fMRI resting state (124,125). It assigns a latent state to each time point. The possible downside of this method is that it requires to specify how many latent states there are present in the data. Furthermore, there will be a greater chance of state transitions at time-points of non-stationarities.

Temporal ICA: identifying components of similar spatial configuration through

time (126). Compared to HMM or k-mean clustering techniques, it allows for multiple components to be involved at a specific time point. How to further quantify this representation is not always apparent.

Spatial distance weighted correlation: A method where each time-point receives a weight vector to be subsequently employed in a weighted Pearson correlation. See §3.2.3.1, *Paper IV* and *Paper VIII* for more details.

Other methods: There are many other variants and derivatives of the methods mentioned above. And there are other additional methods that could fall into their own category. Some of these proposed methods include using: eigenconnectivities with sliding windows (127), Kalman filters (128), sliding window ICA (129), dynamic conditional correlation (130), wavelet coherence (60,131,132).

2.3.2 Parameter choices for the different methods

Different methods have different parameters that must be set prior to analysing the data. Model parameters can be optimized but with a lack of ground truth in dynamic functional connectivity it makes the process difficult (i.e. we do not yet know what the truth in the brain is). It entails some uncertainty regarding what is being optimized when fitting a parameter (e.g. the optimization may make the analysis more sensitive to the neuronal signal or noise like head-movement artefacts). Some parameters can effect the method in very large ways.

Regarding the sliding window method, the window length parameter needs to be chosen. This can drastically effect the results. It is hard to know for sure what the optimal window length . The current praxis is to use a rule of thumb (133). Many of the other methods listed above needs the researcher to specify how many states or components (often denoted as k) are present in the data. Current estimates range from 2 (see (134)) to 17 (see (135)) with many values in between. This becomes problematic as results may be biased by what assumption that are made for community detection. This issue is problematic

and more work is required to determine what a reasonable choice of k is.

2.3.3 Which dynamic connectivity measure is best?

The different methods make very different assumptions about how to derive estimates of temporal change in connectivity. HMMs use only one time point (at $t-1$) to assist the state assignment of t. The sliding window methods have to use $t - \frac{w}{2}$ to $t - \frac{w}{2}$ of points to estimate the connectivity at t, where w is the window length parameter . The spatial distance method uses all time points but weights them based on their spatial similarity. These different assumptions are discussed in more detail in *Paper VIII*. However, given these different methods, the obvious question is: which method performs best?

Currently two studies compare different methods of dynamic functional connectivity. The first is by Shakil et al (136) which aimed to show that the sliding window method is sensitive to state transitions. A downside of these simulations is that they focus primarily on non-linear state shifts, and these types of shifts in the BOLD time series are thought to be primarily due to noise (52). The second study is included in this thesis (*Paper IX*). Here, from comparing five different methods,[5] we found that the spatial distance and jackknife correlation methods perform much better than sliding window and tapered sliding window methods when estimating a fluctuating covariance parameter. The temporal derivative method came in at third place. Other studies have demonstrated problems with the sliding window methods through simulations (e.g. (137)), but do not compare their results in relation to other methods.

[5]The five methods are: sliding window, tapered sliding window, spatial distance, jackknife correlation, temporal derivative.

2.3.4 The structure of dynamic functional connectivity representations

Since dynamic functional connectivity creates a representation that will then be quantified, it is important to consider what these different representations look like. Different methodologies can lead to different representations, with a different number and types of dimensions left in the data. This fact is important for which subsequent analysis steps can be performed. Three of the most common representations include:

Connectivity time series: Each edge is a time series of connectivity estimates. (Methods: sliding window, tapered sliding window, temporal derivative, jackknife)

Components: Each component is expressed to a certain proportion per time point (Methods: temporal ICA)

States: Each time point is assigned to one specific state or latent variable (Methods: HMM, k-means).

The one universal property in these very different types of representations is that they are all expressed over time.

Some studies first use one kind of method to derive one of the representation forms described above and then subsequently perform additional step to transform it to another form. For example, the connectivity time series computed in (119) are subsequently clustered into states using k-means. Conversely, *Paper III* clustered (using k-means) the data into states and used k number of states to infer a discrete connectivity time series.

Recording of multiple connectivity time series allow for a connectivity matrix to be created at each time point. There are multiple ways researchers might refer to "a connectivity matrix at time t". Some refer to it as a *graphlet* (the origin

of which seems to be (138)) but some dislike it as it can be confused with the term graphlet in static network theory. Others prefer *snapshot representation* (139) or *supra-adjacency matrix* (140). In this thesis the term graphlet is chosen. It is possible to have connectivity matrices over other dimensions than time. In this thesis, apart from time, graphlets are also considered over states and frequencies. To this end, the papers in the thesis often say what type of graphlet it is (e.g. time-graphlet or state-graphlet).

2.3.5 Applications of dynamic functional connectivity

Unfortunately most applications of dynamic functional connectivity in contexts outside of methodological research have used the sliding window method. When subsequently quantifying a dynamic representation there are several options. Aside from temporal network theory (see §2.5), researchers often quantify the variance of the signal or assign connectivity representations to states. As eluded to in §2.1, these methods of quantifying dynamic fluctuations can be problematic (see §3.3 for full discussion). Given these considerations, it is hard to evaluate which of the studies listed below are actually quantifying dynamic fluctuations. Unless all issues regarding chosen methodology, variance differences between edges, movement (52), are adequately controlled for, all dynamic functional connectivity studies failing to do this should be interpreted with great caution.

With this disclaimer stated, like its static counterpart, dynamic functional connectivity estimates has been applied to a number of questions regarding both basic properties of the brain, general biological mechanisms, and CNS diseases. Dynamic functional connectivity is being applied to increasing number of topics ranging from development (141–143), attention (144), levels of consciousness (145), creativity (146), and mind-wandering (147,148). In clinical research it has been applied to various disorders that include: depression (149), schizophrenia (150–153), and bipolar disorder (153).

2.3.6 Dynamic fluctuations and neuronal activity.

While dynamic functional connectivity shows promise, there is one key question yet to be addressed: Are studies in dynamic functional connectivity quantifying neuronal activity? If, for a certain imaging modality, this is answered negatively then there is no point to apply dynamic functional connectivity for that imaging modality.

It is perhaps too early to give definitive proof to show that this questions can be answered positively, but that is some evidence in favour. Simulation studies have shown that only modelling based on static functional connectivity are less accurate than simulations considering the dynamic patterns of the BOLD signal (154). There has been a push to demonstrate a neuronal origin of dynamic functional brain connectivity in recent years (118,141,155–158). Here we are seeing signs that the dynamics of the BOLD signal have a neuronal correlate. Further, as stated previously, different MEG frequencies have been associated with different fMRI edges, suggesting different dynamics for the edges (65).

Considering these preliminary positive answers to this question, it follows that there is a high potential for dynamic functional connectivity to be used in wide range of applications from clinical (e.g. able to identify pathology with greater specificity) or more basic neuroscience (e.g. decoding content of cognition).

2.4 Network theory

In this subsection a brief account of network theory will be given. Network theory offers a model of some group of connections. A network is a graph (G),[6] which is a mathematical object defined by a set of nodes (sometimes called vertices in some fields) connected by edges (sometimes called links),

[6]Networks are a subset of graphs, but a rigid definition of necessary conditions to define this subset is rarely used. A network generally points to something that exists in the world or has nodes and/or edges that are given names.

defined as:

$$G = (\mathcal{V}, \mathcal{E})$$

where $\mathcal{V}$ is the set of nodes. The number of nodes in $\mathcal{V}$ is often denoted with N. $\mathcal{E}$ is a set of 2-tuples that represents the edges or connections between each pairs of nodes (i, j) where $i, j \in \mathcal{V}$. The graph can be represented by a connectivity matrix A, which is of NxN in size. Networks can be binary (an edge is present or not), or weighted, with weights or strength coefficients (often normalized between 0 and 1 or -1 and 1) attached to each edge in the connectivity matrix to signify the magnitude of connectivity between each pair of nodes.

One appeal of network theory is the diverse topics it can cover. A set of nodes can be a group of people, a collection of cities, or brain regions. Each element in the nodal set can represent vastly different things in the world (e.g. Ashley, Gothenburg, or the left thalamus). Edges too can represent a range of different types of connections between their respective nodes (e.g. friendship, transportation or neural communication). Regardless of what the nodes and edges map to in the world, similar measures can be used to quantify the network properties. Many different properties regarding the connections between the nodes can be quantified such as a variety of centrality measures, hub detection, small worlds, clustering, efficiency (see (12,159,160) or other sources for discussions about these measures). Broadly speaking, network properties can be in different classes:

Edge measures: a measure relating to each edge.

Nodal measures: a measure relating to each node.

Community measures: a partition of communities or properties of derived communities.

Motifs: Reoccurring subgraph patterns.

Global Measures: one measure for the entire network.

Robustness measures: when and how do the network properties degrade when removing edges.

It is important to state the ontological status of a network. The network of an object or process that exists in the world is merely a model. Like all models, networks can have a good or poor fit to the object of interest in the world. For example, the definition of a node is not always apparent. In fMRI there has been considerations whether voxel level or averages into spheres make better nodes (161). The consequence of these choices can be that a model reflects the world less, giving less accurate estimations of the network and its properties. This entails that any properties derived from poorly derived network say very little about the world.

2.4.1 Network properties in the brain

There are many properties that have been identified in the brain regarding its network properties. In this subsection there will be a brief overview. The focus is mainly on large scale networks.

Network theory has helped to identify communities (i.e. brain networks). These communities are often derived through algorithms that aim to maximize modularity (162). Identifying modular networks in the brain is described in terms of *segregation* and *integration* between different brain areas (12,163,164). While these have been more formally defined (165), they are frequently considered more as conceptual principles regarding brains networks organization. It is generally accepted that there is a trade off between being well connected and the cost of having too many connections, which leads to a segregated modular structures (166).

One of the key features regarding efficient integration and segregation of neuronal information in the brain is the presence of small-world network characteristics. The hallmark of these kinds of networks are that they can efficiently transfer information between different communities compared to other types of network structures (167). They can also (but do not necessarily so) have a scale free property which implies that the efficiency of the network is preserved as it expands or shrinks (168). Small world properties of the brain have been identified in the anatomy (169,170) and functional connectivity (171,172) of large scale networks. This degree of small worldness has been linked to levels of consciousness (173) and have been shown to be impaired in clinical populations including: schizophrenia (174,175), traumatic brain injury (176), Alzheimer's disease (177,178). However, anatomical studies in macaque that trace connections have found more dense networks than small world networks (54).

Small world networks are characterized by the presence of some nodes that have dense connections with nodes outside of their own brain network. These nodes are called hubs. While not necessary in a small world network, heavily connected hubs are often essential for efficient between-network communication. Hubs have been identified in both anatomical (179) and functional networks (180). These hubs can either be well connected with brain network hubs ("provisional hubs") or provide a link between different brain networks ("connector hubs") (181). Although the question of which nodes that should be classified as a hub is not always straightforward as different methods could be used to isolate hubs (182,183).

Studies of anatomical networks have shown that well connected nodes are also connected with each other. This property is compatible, but not necessary part of, a small world structure. This phenomena is known as a rich club architecture (184). It has been suggested that this anatomical rich club structure helps to instantiate functional network activity (41). Regarding well-connected systems, de Pasquale et al (46) found in MEG that the default mode network correlated more with other networks in in the beta band (~20 Hz) frequency range. This gives the default mode network, at a certain frequency, a core

network structure. Rich clubs have been shown to increase in EEG power when target stimuli appear compared to distracting stimuli (Bola et al (185), associating functional rich clubs in the theta band (5-7 Hz)).

However the idea of brain network being modular has been challenged with multiple community structures being detected: Assortative (modular networks), disassortative (communities have more edges outside their community), and core-periphery (a well connected core of nodes) in networks based on both structural and functional connectivity (186). This study advocates the importance of nodes that are only partially well connected (dubbed the middle class).

A different line of research have shown that network properties can reconfigure themselves based on the nature of the tasks being performed. Evidence here originates from investigations in dynamic functional connectivity in MEG and fMRI which show network connectivity changes (43,60). Cole et al demonstrated that, for different tasks, a reconfigurations of hubs between brain networks occurs (187). Regarding integration and segregation of brain networks, Cohen & D'Esposito found that functional networks were less modular during tasks and this scaled with task complexity (188). The idea of flexible functional network patterns is a natural starting point for dynamic functional connectivity and temporal network theory to expand upon.

2.4.2 Different network findings and ideas regarding large-scale networks

In this subsection I reflect on how some key network properties in the brain relate to the idea of modular specialization and distributed processing in the brain, two classical theories of cognition.

In the history of cognitive science there have been a few debates which never seem to get fully resolved or the debate often returns once the theoretical paradigm updates. One of the classic debates in cognitive science is the idea

regarding modular or distributed processing. Fodor's idea of modularity (189) argued that the brain functions in (non-distributed) specialized modules. This allowed an explanation to prevalent functional ideas at the time in cognitive sciences, such as the concept that there exists a universal grammar. Others argued that cognition appeared to be distributed and complex tasks required parallel processing (10,190). This school of thought got called connectionism. It advocated that the brain's distributed structure allowed for complex functional processes, such as language, to be learned. When the neuroimaging research field matured, the idea of distributed processes became the dominant idea within cognitive neuroscience.

Despite the successes for the distributed processing system view on brain function, network theory was used to help restore the spirit of some of Fodor's modularity ideas. Given that brain processes are often distributed, brain areas that were often segregated together could be seen as a distributed modules. The logic is similar to Fodor's original ideas but reformulated with a distributed area receiving a modular function. Modularity, in this sense, retains the idea that the neuronal processing is localized to particular unit—although the functional unit is redefined in terms of modular brain networks. While there are very significant differences between the two types of modularity (see (191) for a discussion), the idea of functional specialization to take place through segregation of information in a modular structure remains (192). Alternatively, the idea of reconfiguring communities within networks can be seen in line with the classic connectionist approach that cognitive processes are instantiated on multiple network configurations. The key difference now is that brain networks loose their functional specificity—at a different time the brain network module has a different function. This dividing line is akin to Model 3 and Model 4 in figure 1.1.

Although these updated ideas of this classic debate are far less antagonistic to each other than the classic debate, they do present different views in how neural or cognitive processes are thought to be organized. In sum, in some ways the classic debates of modularity versus distributed processing have not disappeared. Instead there is a new dividing line regarding how the brain produces

cognitive processes with brain networks that are either flexible or functional specific remains. Temporal network theory has a possibility of finding support for this latter perspective.

2.5 Temporal network theory

Network theory has rather recently seen a shift from single layer to multilayer network models in the last decade (140,193,194). Different layers of networks entail that there can be multiple and different types of edges between the same nodes. A multi-layered network has "layers" over different types of variables, ranging from a different quality of connections (e.g. different types of transportation connections connecting cities (train, sea, road, air), different types of social relationships (trust, friendship), time resolved networks etc.).

This is done by modifying the definition of a network to include edges to be expressed over additional dimensions.

$$G = (\mathcal{V}, \mathcal{E}, \mathcal{D})$$

where $\mathcal{D}$ is a set of the additional non-nodal dimension(s). In a normal Graph outlined in §2.4, each edge in $\mathcal{E}$ is expressed by a 2-tuple which contains indexes to two nodes in $\mathcal{V}$. For example, if there are two cities connected by a transportation link, each edge contains two nodes (city,city). $\mathcal{D}$ contains an additional set of possible edges which an edge can be expressed on. Considering the above example, the type of two cities (nodes) can have an edge along multiple types of transportation (e.g. "rail", "road", "air"). $\mathcal{D}$ will contain these additional three types of transportation, meaning each edge is expressed as a 3-tuple (city,city,transport-type). $\mathcal{D}$ can contain temporal index {"2014","2015","2016"} expressing when an edge is present. It is also possible for both transportation type and temporal indexes to be included. A temporal network is when $\mathcal{D}$ is, or contains, an ordered set containing time indices.

Multilayer networks depictions of the human connectome will be needed across multiple different dimensions, such as task context, frequency and time (see *Paper IV* for discussion. See also (195)). In a similar way to functional connectivity being restrained to the structural level, dynamic connectivity is restrained to the functional level.

2.5.1 Applications of temporal network theory

Most measures in temporal network theory can be expressed in a similar way as network theory (e.g. per node, per edge). Obviously, measures can now be expressed per time point also. Further, there are also hyper measures, which are correlations of connectivity matrices (hypergraphs) or edges (hyperedges).

The applications and research questions that temporal network theory have been applied to are diverse. Quite often edges are shown as distributions of the time intervals between when the edge was active. A discussion of some different aspects of temporal networks and their application outside of neuroscience is given below.

2.5.1.1 Distributions of communication

When and how often different edges communicate is a large part of temporal network theory. This property is often quantified for each edge. One widely investigated pattern is a "bursty" pattern of communication. A bursty pattern is characterized by multiple brief intervals between connections combined with varying longer periods in between connections. This is often considered to be "scale free" temporal communication as the distribution becomes similar, regardless of which temporal scale is considered. Temporal communication distributions are often modelled as a heavy tailed statistical distribution or compared with a Poisson distribution. This suggests that, when there is an instance of connectivity, the probability of it being followed by additional instances of connectivity is high. A non-Poisson (often heavy-tailed) distribution has been widely reported across different social and biological phenomena ranging from email communication (196), telephone communication (197), group

membership (198), human interactions (199), epidemics and spreading dynamics (200,201), cattle trade movements (202), and soliciting online prostitution (203).

Bursts can originate for multiple reasons. Underlying mechanisms behind the heavy tailed distribution include a queuing processes (196), cascading non-homogeneous Poisson process (204), and a self exciting Hawkes process (205). These different ways of modelling the distribution of connections is related to different hypotheses for why such patterns of communication occur.

2.5.1.2 Dynamic communities

Detecting evolving communities in a network is an active part of research within temporal network theory. The idea here is that the cooperation of different parts of the network can reconfigure over time. Multiple algorithms have been proposed in order to best identify dynamic communities (206–210). This methodology has been applied to numerous different research questions including: emergence of subfields in citation networks (207), voting patterns in the United Nations (211), social networks (212), and migration patterns (213).

2.5.1.3 Paths and reachability

Temporal paths lengths can reveal the time it takes for information to spread through the network. Centrality measures in dynamic processes can identify which parts of the network are critical for unhindered passage of information flow. It has been shown that removing nodes with high centrality slow down the spreading of information in temporal networks (214). Temporal betweenness centrality and temporal closeness centrality were used in studies of e-mail communication to identify important nodes of information flow (215). Temporal betweenness centrality has also been used to identify changing relationships between venture capitalists (216). A temporal extension to PageRank algorithm, called TempoRank, has been applied to human interaction (217). Reachability metrics can be used to see if and how many temporal paths are present in communication with e-mails and in online dating communities (218).

2.5.2 Why temporal network theory is needed for neuroscience

Just as the network approach argues that focusing on specific regions of the brain will not be sufficient to provide a full understanding of cognitive processes, the same might be said that the static functional connectivity and network theory alone might not be sufficient to understand human brain function. Thus there has been a growing interest in understanding dynamic processes of the brain. Similarly to the concept of the human connectome for mapping static functional connectivity, the analogous goal within dynamic functional connectivity has been dubbed the "dynome" (219).

The idea that static functions connectivity and network theory being too insensitive in cognitive neuroscience is argued in *Paper IV* with regards to the study of clinical populations:

> "alterations in static default mode network connectivity have been implicated in: depression (Sheline et al. (2009), Hamilton et al. (2012)), schizophrenia (Garrity et al. (2007), Pomarol-Clotet et al. (2008)), traumatic brain injury (Bonnelle et al. (2011), Sharp et al. (2011), Thompson, Thelin, Lilja, Bellander, & Fransson (2016)), obsessive-compulsive disorder (E. R. Stern, Fitzgerald, Welsh, Abelson, & Taylor (2012)), autism (Cherkassky, Kana, Keller, & Just (2006), Weng et al. (2010)), fibromyalgia (Napadow et al. (2010), Flodin et al. (2014)), post-traumatic stress (R. K. Sripada et al. (2012)) and Alzheimer's disease (Greicius, Srivastava, Reiss, & Menon (2004)). This is not an exhaustive list. This list suggests that it is very difficult to make inferences regarding static differences in connectivity in the default network that are specific to a particular patient cohort." — *Paper IV*

We are left with two possible conclusions regarding the limitation of specificity regarding static functional networks:

1. There is a temporal-spatial limitation due to imaging modalities that prevent greater specificity.
2. There are simplifications in the assumptions of the static network analysis which hamper specificity.

Regarding the first possibility, improving imaging modalities, such as using 7T fMRI to identify functional connectivity, will increase spatial specificity (220–222). High temporal resolution with MEG or ECoG may also have their respective benefits (but also caveats).

Despite these improvements, increasing the spatial or temporal resolutions alone may not be sufficient. Temporal network theory removes the simplifications of network theory that the network is constant through time. In this perspective cognitive processes are no longer associated with a distributed pattern. Instead it becomes a distributed pattern embedded through time (Model 4 in §1.2). With temporal network theory there is the potential for an increased specificity to network properties regarding the greater questions regarding cognitive processes. Speculatively, this may provide insight into the following areas:

1. Greater sensitivity to differentiate and classify between disorders of the CNS.
2. Reveal differences in individual behavioural strategies.
3. Greater sensitivity to underlying neuronal mechanisms.
4. Greater understanding for the integration of information between segregated networks in the brain.
5. Insight into the temporal structure of cognitive processes.

If any or all of these five different possible promises of temporal network theory can be fulfilled is an empirical question that has not yet been answered. However, as we have shown, there are some positive answers to these. Some tentative answers are given in §2.5.3 and §3.3.4

2.5.3 Applications of temporal network theory within network neuroscience

Studying dynamic networks is still a relatively new field of research. A large majority of analysis methods have considered the fluctuations of network communities during different tasks. It is however important to not that the studies listed in this subsection sometimes use different time scales. Some compare networks developing through a trial while others use the trial length as the time unit for the temporal networks (which can make the results between the two hard to compare). Further, most studies use a version of the sliding window approach which, as noted earlier, performs inaccurately. Like network theory, models in temporal network theory share the same ontological status. The goodness of their fit with what they model depends on the derivation of the representation.

Some basic properties of the brain have been studied, finding dynamic fluctuations correlate with high or low modularity (223). Studies have been carried out to address community reconfiguration for multiple cognitive faculties, including: working memory (224), learning (131,225–227), changes during development (228), language (229) and mood (132). A slightly alternative approach is to identify communities of edges which correlate through time (hyperedges) (230).

Instead of using temporal network theory, others have performed static network theory measures repeatedly through time (185,231). This results in a time series of network measures which can be used to identify temporal network characteristics. While studies are not explicitly creating a temporal network object, they can be formulated as temporal networks and the measures are properties derived per time point.

From the dynamic systems approach, criticality and avalanches have been observed in fMRI data (122), EEG (232) and MEG (233). Metastability and a dynamic connectivity derivation has also been linked to rich clubs across different tasks compared to rest (234).

2.6 Tools for funcitonal connectivity and network quantification

For historic reasons, the development of tools for network analysis with neuroimaging has heavily relied on the Matlab (Mathworks Inc.) scientific programming environment. Many imaging modalities have most their established software written in Matlab. These include *SPM* (235), *Fieldtrip* (236), *Brainstorm* (237), *EEGLab* (238), and *HOMER2* (239), analysis tools that collectively can analyse MEG, EEG, fMRI, PET, fNIRS, ECoG and other types of invasive electrophysiology. To quantify networks, the *Brain Connectivity Toolbox* (240) is frequently used. Some of the aforementioned software packages have released standalone software for which a Matlab licence is not required, and most software developers aim to not require additional commercial toolboxes to be installed.

Python is an established tool for scientific data analysis. Neuroimaging has been lagging behind other fields with regards to using Python. There is active amount of software development in Python: which includes: *MNE python* (241), *Nipy*,[7], *Nipype* (242), *Nibabel*,[8] and *Nilearn* (243). Some of the software reproduce functions that already exists in other languages and others are only wrappers for other software. There are additional benefits that Python offers. For example, better visualization tools such as *pycortex* (244).

There are many benefits to open and free software. It makes the tools of research more accessible. With greater accessibility, it also allows for a greater chance for people to contribute to the code, making improvements on what others have previously done.

With regard to software tools for calculating network metrics and visualize the results, *iGraph* is software for C, R and Python (245), *NetworkX* for python (246). For the purpose of visualization of networks, *Cytoscape* (247) and *Pajek* (248) are publicly available and both are standalone applications. In the

[7]https://github.com/nipy/nipy
[8]https://github.com/nipy/nibabel

programming language R, *network* (249), *NetBioV* (250), and *BioNet* (251) are packages available for network theory. While there are established, well documented tools for network theory, selection of available analysis tools become a more scarce for temporal network theory. Two packages that exist are *TQ* for python[9] and *networkDynamic* for R.[10] *NetworkX* is also able to handle multi-layer networks. Multilayer network library can plot multilayer networks and perform some analyses.[11]

My personal opinion is that tools temporal network theory is inaccessible for many with limited programming experience, as it becomes hard to see wide adoption of temporal network theory by researchers unless different tools are available and simplifying the integration with other tools or even to derive the network representation. Taking the above into consideration, in *Paper IV*, the Python package *Teneto* which aims to derive, analyse and plot temporal networks was designed to be compatible for cognitive neuroscience goals (see §3.5).

[9]https://vladowiki.fmf.uni-lj.si/doku.php?id=tq
[10]https://cran.r-project.org/package=networkDynamic
[11]https://mkivela.com/2015/12/11/multilayer-networks-library/

Chapter 3

Works in this thesis.

3.1 Introduction

Following the overview of functional connectivity and network theory in §2, this chapter describes and contextualizes the articles included in this thesis. The work can be divided into four different overlapping themes:

Theme 1: How to derive estimates of dynamic functional connectivity.

Theme 2: Applying temporal network theory onto functional neuroimaging data.

Theme 3: Considering other types of multi-layer networks other than time (frequency) and functional connectivity on different time scales (rehabilitation after trauma).

Theme 4: Creating software tools to facilitate and improve research for themes 1-3.

3.2 Theme 1: deriving estimates of dynamic functional brain connectivity.

In §2 some of the common methods for dynamic functional connectivity were outlined. Several of the papers included in this thesis advance different aspects of the interpretation, derivation, and preprocessing of dynamic functional connectivity.

3.2.1 What is "high dynamic connectivity"?

In static functional connectivity or structural connectivity, identifying high connectivity is rather straightforward: if an edge has a higher correlation than two other time series, there is more communication. This is because of the fundamental functional connectivity assumption outlined in the §2.1.1. The magnitude of the correlation is the most relevant aspect for performing an analysis or making comparisons between different groups with static functional brain connectivity.

One problem with dynamic functional connectivity, that remained undefined for quite some time, concerns what should be considered "high", "low" or "interesting" dynamic connectivity. Perhaps due to obvious nature of high connectivity in static functional connectivity, many do not consider this issue relevant. In one of the previously published reviews of dynamic functional brain connectivity, it was stated "it is natural to expect that FC metrics computed on fMRI data will exhibit variation over time" ((252), p. 361). The problem is that there are multiple ways to identify a "variation over time". I believe this question was not addressed in the dynamic functional connectivity literature until *Paper I*.

To expand upon the idea, in dynamic functional connectivity, many methods result in there being multiple connectivity time series. These connectivity time series will have their own fluctuations in connectivity. They can oscil-

late around different means and have different variances. If we want to find "interesting" dynamic functional connectivity, it is important to keep in mind that there are different properties and some could be effected by non-dynamic sources. The crux of the problem is that what is "interesting" for one time series may not be interesting for another.

Consider the following analogy which is also illustrated in **Figure 3.1**: there are three friends Ashley (A), Blake (B), and Casey (C). They talk to each other everyday. A and B talk to each once every hour between 10.00 and 22.00. A and C talk to each other once a day (at noon exactly). Around 18.30 on one day, both A-B and A-C communicate. The rest of the day is as normal. How to go about answering the question "which event is more interesting at 1830: A-B or A-C?" In absolute terms, A-B will have communicated 13 times that day, and A-C will have communicated only 2 times. Between 18.00 and 19.00, A-B will have communicated three times more than A-C. Considering the highest frequency of events leaves us with the conclusion that A-B communication was the most interesting. However, we expected 12 connections between A-B and 1 connection between A-C over the course of the day. This entails we have a 100% increase in expected communication for A-C whereas there was only a 8.3% increase in expected communication for A-B. Despite communicating less, the A-C's communication was less expected, and could therefore be considered more interesting. This illustrates that there are at least two possible ways to consider which of these two events was more interesting than the other.

This issues related back to the underlying assumption of functional connectivity (see §2.2.1): a larger correlation entails more communication. When extending this to a temporal scale, it is hard to directly translate this. The two alternatives from the example above can use this assumption:

1. A larger correlation (magnitude) entails more communication.
2. A larger correlation than expected entails more communication.

This uncertainty regarding how to extend the functional connectivity assumption is explored in *Paper I*. Here it states that there are at least two thresh-

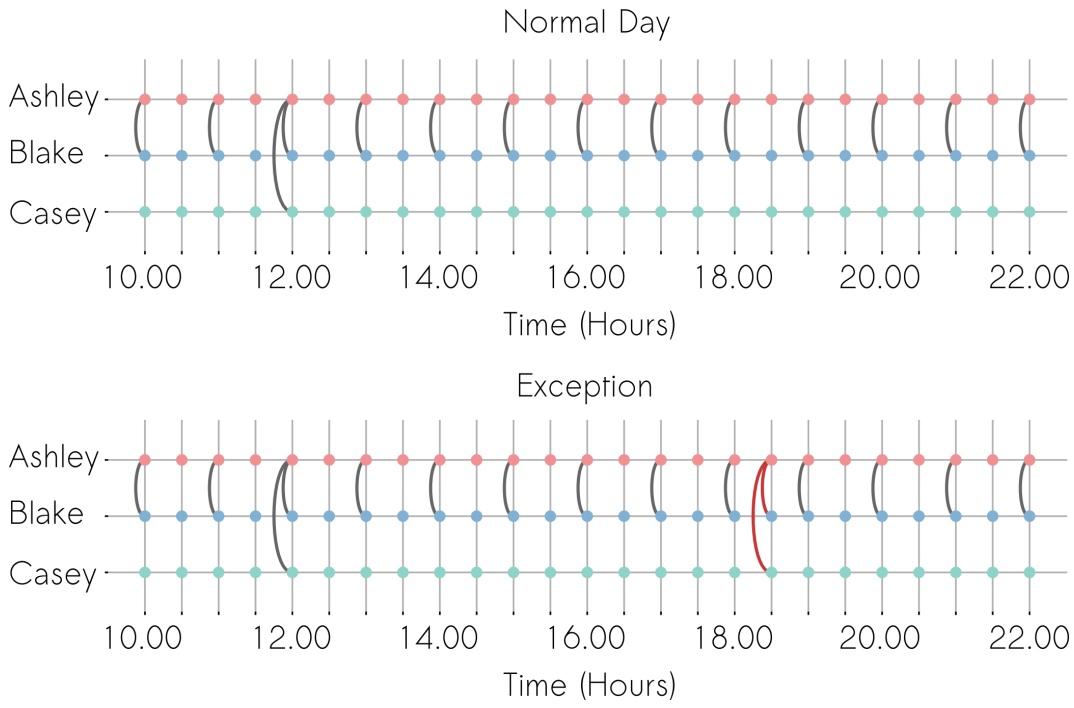

Figure 3.1: An illustration of what should be considered interesting dynamic functional connectivity. Top: The everyday scenario. Each each connection represents an instance of communication. Bottom: Two additional connections have been added (marked in red). One possibility is to see the new connection between Ashley and Blake be considered more import than Ashley and Casey (because there are more connections). Alternatively, new communication between Ashley and Casey can be seen as more important as there is a larger increase in expected communication.

old strategies for dynamic functional connectivity. Here a threshold strategy means what type of criteria should be used to differentiate between interesting and non-interesting activity (but not necessarily where the line should be drawn). While *Paper I* considers two strategies, it can be expanded into three difference strategies:

1. *Magnitude based threshold:* time points of an edge with the highest covariance relationship are considered to be the most interesting.

2. *Within time series variance threshold:* Time points that deviate from the mean connectivity relative to its own time series are the most interesting. Connectivity deviation is based on the time series' own variance.

3. *Global variance threshold:* Differences in connectivity that deviate a specified amount from a common mean for all time series (i.e. mean at 0). The threshold is set to be the same for all time series.

Based on which threshold strategy is chosen, different edges in the brain will be considered as "interesting". In *Paper I* the magnitude based threshold perspective will lead to more interesting activity within brain networks. On the other hand, with the global variance threshold perspective, there will be more between brain network connectivity marked as interesting. Finally, the within time series variance threshold avoids the mean-variance biasing problem as every edge gets evaluated independently of all other edges. However, it has its own downsides. Unless some constraint of plausible edges is placed on the network, then there is a high change there will false positives where edges with no possible communication will have some edges marked as interesting. Such constraints are possible avenues of future research.

This implies that all three perspectives have their downsides and it becomes critical that researchers using dynamic functional brain connectivity methods reflect upon the fact whether their decision might have influenced their results (an example of this is given later). When applying line of reasoning this to brain connectivity, the question is whether the magnitude of the covariance matters,

or whether two brain areas increase their covariance in relation to their typical relationship. More work is needed to better characterize the implications from using different perspectives/threshold strategies.

One weakness in *Paper I* is that it did not stabilize the signal variance of connectivity time series. This may have lead to a misleading result between mean and variance. The problem of variance stability of time series of functional connectivity was later addressed and corrected in *Paper II*. The consequences of *Paper I* about what should considered interesting dynamic functional connectivity remained. All papers published in dynamic functional brain connectivity are effected by this mean-variance dilemma and researchers need to take it into account.

3.2.2 Regarding the stability of the variance in connectivity time series.

Interesting features of dynamic functional connectivity can be related to the variance of the connectivity time series. This entails that the variance must be as unbiased as possible.

When estimating a correlation, the variance may become biased. This will be exemplified in the following scenario: If the "true" correlation between two variables (x_1 and x_2) was 0.3 and the "true" correlation between two other variables (x_3 and x_4) was 0.95. A set of studies investigating these variables will estimate a set of correlation estimates between these variables. All things being equal, we will expect to see greater variance around the sample mean between x_1 and x_2. This is because the variance of a Pearson correlation is not stable.[1] This is often corrected for by an approximating stability, often achieved with a Fisher transformation. This means the expected variance around the two variable pairings become approximately the same. A consequence of the Fisher transform is that it attempts to remove the skewness that is caused from the

[1]Fisher described this as to "cramp all the high values of the correlation into the small space of $r = 1$" (253).

above phenomena, often creating approximate Gaussian distributions around a sample mean.

Drawing samples from a population is different from the intended function of dynamic functional connectivity. In dynamic functional connectivity the idea is the true correlation value is fluctuating. Additionally, dynamic functional connectivity has multiple connectivity time series. Thus, in dynamic functional connectivity, there are two concerns regarding the stability of the variance:

1. The within connectivity time series variance stability.
2. The between connectivity time series variance stability.

To illustrate the difference between these two concepts, *Figure 3.2* shows four different scenarios with differing variances distributions. The problem of variance instability is that an estimate behaves differently based on where its correlation estimate lies. We can clearly see that if both time series are skewed in a similar way (first scenario) this is not problematic when comparing between the time series.[2] However, the variance is different for different correlation estimates when looking within the time series. If the time series have symmetric distributions (like scenario 2 and 3) then this entails within time series stability. This is because the tails of the distribution in both low and high connectivity behave in a similar way. If however the variances of these time series are different *and* these variance differences are due to the correlation estimate, then is not stable between time series. With similar variances and symmetric distributions (Scenario 3) then they are stable in both regards. The final scenario shows when there is no variance stability.

In *Paper II* we reasoned that within time series variance is what should be achieved. The motivation for this is that it has less bias on subsequent analysis steps (e.g. clustering; see §3.2.6). It also make local variance thresholding

[2]For example, considering all values above the mean of the distributions in scenario 1 of Figure 3.1 will select similar values between the two time series. This would not be the case in scenario 4 (different number of values and have different variances) or scenario 2 (the variance of the value in time series 1 would be greater).

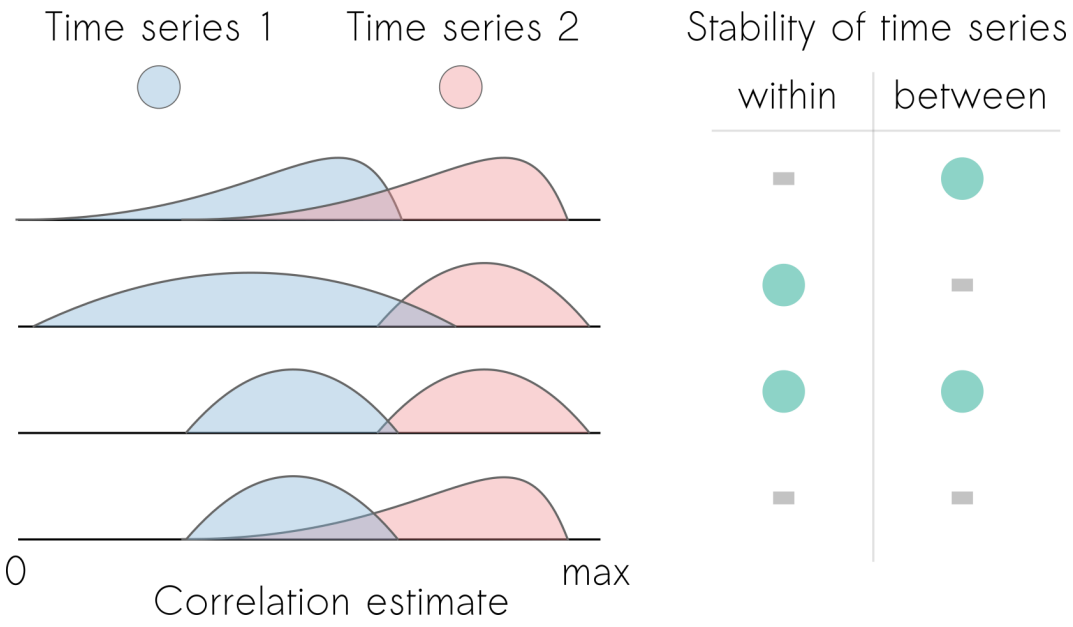

Figure 3.2: Illustration of different types of variance stability that are possible with dynamic functional connectivity. Left: four different scenarios with different distributions of the connectivity estimates within different time series. Right: table depicts whether the variance of the time series is stable within and/or between the time series for the corresponding scenario on the left.

possible (see §3.2.1). By achieving within time series stability, it is also easier to transform the time series to create between time series stability. The other direction (i.e. transforming to between time series stability and then transforming to within time series stability) would be considerably harder.

The use of the Fisher transform is motivated in many dynamic functional connectivity studies to counter the problem of "stabilizing the variance". Thus, we evaluated how it performs in *Paper II* and contrasted it with additional transformation possibilities: the Box Cox transform (254) and a combination of Fisher transformation and Box Cox transformation.

There are several ways the stability of the time series can be quantified. As both of these transformations generally approximate their values to a Gaussian distribution. In *Paper II* we did this in three different ways:

1. Calculating the skewness of the distribution of connectivity estimates of each connectivity time series.

2. Calculate the Shapiro–Wilks statistic which tests against the null hypothesis that the distribution is Gaussian (which has table variance).
3. Comparing the different of the variance within each time series after a median split.

We found that the combined Fisher transform and Box Cox transform approach performed the best. These tests are not sufficient to statistically infer a Gaussian distributions because there are other distributions that are symmetric, have low difference in median split variance, and failing to reject the null hypothesis does not prove the null hypothesis. However, together, they at least give a description or indication of a more stable within time series variances, and these will approximate to a Gaussian distribution.

In *Paper II* we only used the sliding window method to test whether variance became stabilized. When calculating the Box-Cox transformation a parameter has to be fit (λ). When testing with other dynamic connectivity measures, it appears that unless the parameter space of λ is restrained to a certain window, a large λ value is sometimes chosen, transforming the entire time series to a single value. Further investigations into stabilizing variance with other methodologies is needed.

3.2.3 Spatial distance and jackknife methodologies.

Dynamic functional brain connectivity can be derived with many different methods (see §2.3). This list contains two methods: spatial patterns and the jackknife correlation methods where three papers in this thesis developed these ideas further (*Paper III*, *Paper IV*, *Paper IX*). The motivation for focusing on these two different methodologies is to derive connectivity estimates that retain the largest possible temporal sensitivity.

3.2.3.1 Spatial distance methods.

In *Paper III*, the methodology to derive a connectivity time series was developed in two steps. First, the spatial dimensions were clustered into k number

of clusters (in *Paper III* $k = 8$). The covariance for all data-points in each cluster were first derived. The resulting estimates of covariance were then reinserted into the time series. Different dynamic properties could subsequently be quantified (see theme 2). The drawback with the method based on spatial distance presented in *Paper III* was that there were only k number of unique values that the connectivity time series could take.

Paper IV improved upon the previous derivation of connectivity time series described in *Paper III*. Instead of calculating a discrete number of clusters, it treats each time point as the central position in state space and weights all other time points based on by their distance to create a unique connectivity estimate per time point (see *Paper IV* and *Paper VIII* for more details). The distance is based on all nodes/regions of interest per time point. It uses the same rationale as the sliding window but, crucially, uses time points which are similar in space rather than time. This entails that time points anywhere within the time series can be used, which makes sense if the brain is assumed to return to a similar network configuration at some time in the future. Rejecting this assumption would be strange as it entails that the brain cannot ever return to the same configuration. By using time points that are further away in time to estimate the correlation, it increases the sensitivity to detecting differences in connectivity between nearby time points (see *Paper VIII*).

This method derives dynamic connectivity in a different way than the more popular sliding window method. The sliding window method is appropriate in many situations (i.e. when little difference is expected between adjacent time points). In fMRI more than a minute might be needed to accurately resolve a specific time point with the sliding window method. If fMRI is able to track fluctuations in ongoing cognition, the time scales will be shorter than this.

3.2.3.2 Jackknife correlation.

In *Paper IX* the jackknife correlation method to analyse fMRI time series was implemented. The jackknife correlation method is described in even greater detail in (121) and can be seen as a way to create a sliding window with a window length of 1 time-unit.

The jackknife correlation offers an estimate of connectivity for a single time point. The reason why the jackknife trick is needed is because the covariance cannot be defined with a single point. The jackknife trick is that all points but t are used to estimate the connectivity at t (i.e. a leave-1-out strategy). This becomes an inverted approximation of the a single time point correlation.[3]

With one point, there are an infinite equally good lines that can be drawn. A correlation coefficient is impossible to estimate. So it is impossible to have a sliding window method with a window length of 1. However there is a strong relationship between the leave-n-out and a window length of n. Correlating these sliding window time series, after correcting for the inversion, if n is sufficiently large for both methods. This relationship breaks down when n is very high (close to the length of the time series) or close to 1. When n is very high, the relationship breaks down because the leave-n-out method has few time points. The window length of n method is still valid. When n is low the reverse occurs. The window length of n is using very few points to estimate its correlations, and the leave-n-out method is still performing fine. This entails that the jackknife correlation (i.e. leave-1-out) is the best possible sliding window for maximizing temporal sensitivity and uses all but point to estimate the time series.

An interesting property of the jackknife correlation however is that it derives estimates that are relative to every other estimate within the time series[4]. This entails that there is variance compression (see (121)) but this can easily be accounted for with a within time series variance thresholding method (but makes the other thresholding strategies hard). A jackknife estimate of 0.1 is irrelevant in and of itself. However, if it is given meaning when the connectivity estimate is larger or smaller than the other points' estimates.[5]

[3]The inversion is corrected for by multiplying the entire connectivity time series by -1.

[4]This idea is developed more in *Paper IX*.

[5]The same intuition can be applied to derive single time point covariance without the jackknife correlation. The aim is derive a relationship between x_1 and x_2. The mean and standard deviation are needed for both variables when calculating the Pearson correlation. These cannot be estimated when there is only one value (the mean of a single value x_1 is x_1, so the covariance formula will then include x_1-x_1 – which is problematic). We can however assign values that act as the mean and standard deviation of the values of x_1 and x_2. Let μ_{x1}

The spatial distance and jackknife methods are based on very different assumptions, yet these methods correlate highly with each other (see *Paper IX*). Both the jackknife correlation and spatial distance methods give a unique connectivity estimate per time point. The consequence of this property is that non-neuronal noise will most likely be retained at the time point level (instead of being smeared our over time, as it is done for the sliding window method). This means that additional preprocessing steps to remove or scrub time points with high movement may be needed after deriving time series of dynamic functional connectivity.

3.2.4 Unifying the formulation of different dynamic functional connectivity methods.

The methods for dynamic functional connectivity listed in §2.3 vary greatly from each other. Depending on which method is chosen, they can produce profoundly different results. This difference in results is mainly due to the methods using different assumptions. Then it is important for methods to reflect and be transparent about the assumptions they make to be able to interpret the results. *Paper VIII* tries to illustrate in which ways the different methods differ from each other in their underlying assumptions of the data and how they can be brought into a common mathematical framework. In the case of all methods that use a Pearson correlation to derive the connectivity estimate, they can all be easily reformulated into a weighted Pearson correla-

and μ_{x2} equal any other value but x_1 and x_2 respectively. Let σ_{x1} and σ_{x2} equal any other value but 0. These values are set for all points in x_1 and x_2. Conceptually, this is saying that from a set of infinity possible lines we could draw through a single point, we promise to draw the same type of line through every single point. Now let us assume that σ_{x1} and σ_{x2} are both equal to 1 and that μ_{x1} and μ_{x2} are both equal to 0. This entails that the connectivity estimate could be: x_1 multiplied by x_2, given an assumption of stationarity of the time series and the two time series are scaled to have equal variances, these parameters will give connectivity estimates that correlate highly with the jackknife correlation estimates. This is a computationally quicker strategy than the jackknife correlation. This allows for easy real-time dynamic connectivity estimates. This alternative has not been fully explored within the works in this thesis but it shows promise. Its simplicity and counter-intuitiveness may however entail researchers do not want to adopt it.

tion where different methods differ only in values given in the weight vector for each time point. We then generalized this idea so that also methods that do not rely on Pearson correlation can formulated in the weight-vector notation.

These issues are discussed in *Paper VIII* where we state that a general formulation of the derivation of dynamic functional connectivity can be given as:

$$y = R(U(x); w)$$

where y is the dynamic connectivity estimates and x is the raw time series data. R is a relational function (such as a Pearson correlation or hidden Markov model). w are the weights that are to be considered by the relational function. U is a transformation (such as finding the principle components (with PCA) or taking the derivative of the data). This formulation is very abstract but many methods can be formulated in this way. The benefit of such formulation is that the different assumptions used, especially the weights used to derive the dynamic connectivity, become explicitly stated. This allows for different methodologies to be contrasted easily based on how and why they are deriving their connectivity estimates.

3.2.5 Benchmarking different dynamic functional connectivity methods

Many of the different methods for estimation of dynamic functional connectivity are often justified on the basis of simulations. However, it becomes problematic when studies use different types of simulations to characterize and justify their method of choice. For a researcher who is interested to apply a dynamic functional connectivity analysis, it becomes impossible to know which method is best suited for his/her data and needs. *Paper IX* attempted to create a battery of simulation tests which other researchers can use for the purpose of benchmarking their preferred choice of analysis against other avail-

able methods. This equal evaluation process will allow others to see which method should be chosen.

In the benchmarking study different methods to compute dynamic functional brain connectivity were compared. We identified crucial features that all methods need to fulfill, namely to accurately track temporal changes in covariance, the ability of different methods to cope with non-stationarities of the haemodynamic response functions (HRF) that is present in task-related fMRI data, and sensitivity to the possibility of state shifts.

These properties were the basis of 4 different simulations. Additional simulations can be built on top of this and researchers can benchmark their results towards each other. As stated in §2.3.3, the jackknife correlation methods received the best score our simulations, followed closely by the spatial distance method.

3.2.6 Contrasts in dynamic functional connectivity.

In this subsection the consequences of §3.2.1 and §3.2.2 will be clarified regarding further quantifying properties of dynamic connectivity with emphasis on the mean-variance bias and variance stability. This is an important issue as it calls into question the validity of many results that currently claim to be quantifying dynamic functional connectivity.

After deriving estimates dynamic functional connectivity, some further step is needed to make an inference about the representation. We know that there is a relationship between the mean of a connectivity time series, the variance of that time series, and the degree of functional connectivity of that time series (these relationships are clearly demonstrated in *Paper I* and *Paper II*, and it has also been identified elsewhere (223)). The dependence of the mean and covariance on dynamic connectivity estimates may lead to serious problems if one, for example, attempts to contrast estimates of dynamic functional connectivity in one cohort against values obtained from another group if there are underlying differences in static functional connectivity. Two problematic

practices regarding contrasts currently exist:

The problem with quantifying the variance of correlation: A common strategy that has appeared in dynamic functional connectivity studies is to compare the variance or standard deviation of the connectivity time series between some condition or group. This is an easy way to quantify the results and easy to understand. It is however heavily biased by the underlying functional connectivity. If group 1 has an increase in static functional connectivity in some set of edges compared to group 2, we will expect that the dynamic functional connectivity edges will have a higher variance in group 2 compared to group 1. This is because of the mean-variance property identified in *Paper I*.[6] This entails that, unless controlled for, differences in static functional connectivity between the groups will be present in the contrast of the dynamic connectivity variances. In the best case, this means there is a bias present in the data. In the worst case, results of these dynamic functional connectivity studies are merely an overly complex method of quantifying static functional connectivity.

The problem with clustering. Instead of quantifying the variance of each connectivity time series, researchers sometimes cluster the time points/graphlets after deriving their dynamic functional connectivity estimates. There is no problem with clustering per se, there is however a problem when the mean and variance of each edge is not normalized appropriately before clustering (e.g. having a mean of 0 and standard deviation of 1). If this normalization is not performed, any functional connectivity differences between groups will be reflected in differing mean and variances of the time series that are being clustered. It should be stressed that simply demeaning the connectivity differences it not sufficient, as it will still lead to differences due to static functional connectivity. To illustrate this, assume that there is only one edge. Group 1 has high functional connectivity and group 2 has low functional connectivity. Here we will expect group 2 to have a higher variance due to underlying functional connectivity differences. Both the raw connectivity time series and the demeaned time series will see clustering behaviour based on this underlying static functional connectivity. Thus, the clustering will be biased by the static

[6]This still holds when the variance is stabilized (see *Paper II*).

functional connectivity difference. All subsequent analysis will again either be biased or merely quantifying static functional connectivity differences.

In sum, the consequences of some of the methodological work within this thesis calls into question the validity of methods quantifying contrasts with dynamic functional connectivity. Many of the studies cited in §2.3.5 suffer form this problem, as do many other studies not discussed, meaning many perceived dynamic connectivity differences at present may just be functional connectivity differences.

3.2.7 Summary of theme 1.

The work in this thesis has tried to contribute to the field of dynamic functional neuroimaging connectivity research in five different ways.

1. Considered what high or interesting estimates of dynamic functional connectivity could mean (*Paper I*)
2. Evaluated different preprocessing steps to obtain stable and less biased estimates of dynamic functional connectivity (*Paper II*).
3. Applied the spatial distance and jackknife methods to fMRI data combined with the weighted Pearson correlation approach to derive estimates of dynamic functional connectivity with a high temporal sensitivity (*Paper III*, *Paper IV*, *Paper IX*).
4. Clarified how different methods relate to each other in a general but abstract formulation (*Paper VIII*).
5. Contrasted different dynamic functional connectivity methods to investigate how well they can track a fluctuating covariance parameter (*Paper IX*).

3.3 Theme 2. Using temporal network theory on dynamic functional connectivity.

After estimating the dynamic functional connectivity, there are different ways in which these estimates can be further evaluated. In §3.2.6 it was discussed that quantifying the variance or the clustering can be problematic. Temporal network theory is another way to quantify a dynamic functional connectivity representation that was explored in some of the papers in this thesis. If a time series of graphlets has been derived, then temporal network theory can be applied.

3.3.1 Introduction to temporal network theory.

Temporal network theory allows for new properties of the brain's networks to be quantified. By maintaining the temporal sensitivity in the dynamic connectivity representation, we can, for example, examine the flexibility of the brain's functional connections. The application of temporal network theory when applied to functional neuroimaging data is described in *Paper IV*. Temporal network theory can quantify dynamic network properties in numerous ways. Those explored in the papers in this thesis are detailed below.

3.3.2 Bursts

In *Paper III* we quantified whether the temporal pattern edge connectivity displayed a bursty pattern. This analysis was conducted on 100 healthy subjects from the Human Connectome Project (HCP) dataset (255). As discussed in §2.5, a bursty pattern of interaction occurs in many different areas of research. In this paper we were able to show that connectivity appeared to be bursty.

Paper III also found that between brain network communication was more bursty and within brain network communication was more tonic (i.e. always

present) or periodic. This is interesting as it can take the network theory concepts of segregation and integration and interpret them with a temporal perspective. The segregation of brain networks occurs on one time scale (tonic/periodic). The integration of the information between brain networks occurs on another time scale (bursty).

While the above is an appealing hypothesis that was identified in *Paper III*, there is a problem to it. *Paper III* used a magnitude-based thresholding strategy. As stated in Theme 1, the results of connections can be heavily dependent on the thresholding strategies (and may induce a between/within brain network bias). In *Paper IV* we performed the same comparison, on a different dataset (see below), testing how bursty between and within brain network connections were. This time a within time series variance threshold was used. Here we found no difference between within and between brain network connections—both had a bursty pattern. These differences between the results in *Paper III* and those in *Paper IV* are illustrated in *Figure 3.3*. It appears that the difference between different types of communication between networks may have been induced by the magnitude based thresholding.

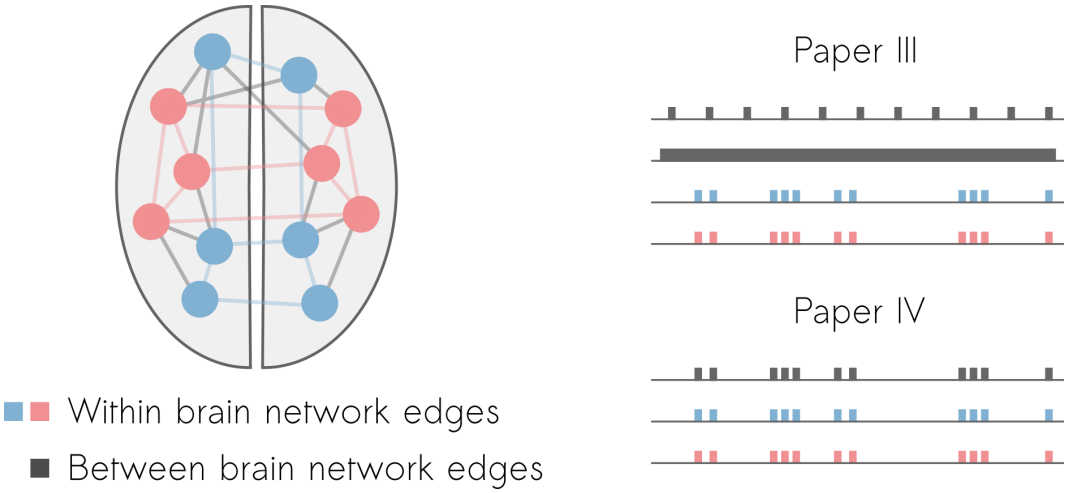

Figure 3.3: Illustration of the differences between Paper III and Paper IV regarding distribution of edges. *Left:* schematic illustration of brain networks showing the differences between within and between brain network edges. *Top-right:* the results in Paper III showed that between network were periodic or tonic. Within brain network edges were bursty. *Bottom-right:* In Paper IV all different types of edges were found to follow a bursty distribution.

In sum, *Paper III* and *Paper IV* found that connectivity time series in fMRI appear to be bursty. *Paper III* identified some evidence that edges between different brain networks were more bursty than edges within a single brain network, but this failed to reproduce with a different thresholding strategy in *Paper IV*.

3.3.3 Temporal paths and reachability

Paper IV explored several global, edge and node based measures applied to resting-state brain connectivity. This paper was exploratory in nature, designed mainly to apply and introduce different metrics of temporal network theory onto dynamic connectivity. An fMRI dataset with 48 subjects (2 excluded) was used. The subjects performed resting state fMRI scans with multiple recording sessions. One session had eyes open, another session had eyes closed (256).

Several between task differences were identified with temporal network theory. While several measures were tested in this exploratory analysis, two metrics will be outlined here which may provide interesting information: closeness centrality and reachability latency. Both of these measure are based on the concept of temporal paths. A temporal path is the time it takes to travel from one node to another. Due to the sluggishness of fMRI, multiple edges were allowed to be travelled per time point.

Closeness centrality is a nodal measure which is high when a node, on average, has short temporal paths. Reachability latency calculates the time taken for a node's temporal paths to reach a certain percentage of all other nodes.

There was a difference in reachability latency between the two conditions (during the eyes closed condition, it took, on average, a longer time to reach all nodes of the brain). Deconstructing these results into brain networks, the largest difference between the two conditions was found in the visual brain network. This shows a potential for temporal network theory to identifying regions which are coupled/de-coupled from the rest of the brain in a specific

task.

When applying closeness centrality, many nodes in the fronto-parietal network had the largest magnitude of centrality. This was the case for both conditions. As the fronto-parietal network is often associated with attentional and executive processes, it makes sense that this network is at the "core" or "temporal hubs" in the brain's dynamic processes.

3.3.4 What needs to be known about temporal networks and the brain

Most of the current work applied to temporal network theory has shown there are differences across different tasks (see §2.5.3). Temporal network theory allows us to try and analyse the brain with a new set of tools. In §2.5.2 it was stated that temporal network theory may provide "insight into the temporal structure of cognitive processes". Given the assumption in §1.2-1.4 of this thesis that understanding the dynamics of the brain will be fundamental to understand its function, this subsection expands a little more on this idea. These ideas are slightly speculative and look to what the potential of temporal network theory can be. This is reflecting on both the knowledge gained in the works of both theme 1 and theme 2 and looks to the future regarding a dynamic network model of the brain. There are unknown mechanisms regarding the the temporal properties of large scale brain networks in the brain that need to be researched. These problems are graphically illustrated in *Figure 3.4*.

The Inference problem: is it possible to infer a presence of brain network at a certain time to be associated with a given cognitive process? Or is it rather a collection or sequence of brain networks that should be considered to be the neuronal correlate for a cognitive process?

The Mereological problem: If two different distributed patterns of brain activity are both associated with a mechanism or psychological correlate and if both of these distributed patterns are active at the same time, is this effect additive

or does a new process emerge?

The Transition problem: When one brain network is active, are transitions to all other brain networks being active next equally possible? Are the transitions between activation of two brain networks "smooth"?

The Stability problem: is it the case that there is a set of "basis communities" that interact in the brain? Or do brain's "basic brain networks" reconfigure to form new communities as a function of time?

The Regularity problem: What is the pattern between different edges or groups of edges reappearing in a temporal sequence of brain networks?

The inference problem is similar to the problem that exists in static network theory. Here there is hope that, when adding a temporal dimension to the analysis, there will be additional specificity in order to make an inference regarding the link between brain networks and cognitive mechanisms. The inference may not be a single brain network to a mechanism, but a sequence of brain networks. Thus, the task set out for temporal network theory is to define models and tests that have a greater ability to detect cognitive processes associated with specific brain networks.

The mereological issue strikes at the heart of the problem between cognition and temporal networks. Do two integrating brain networks merely share their information, or do they, when working together, form something new—a gestalt of cognitive function? It has previously been shown in (257) that different neurons controlling different parts of the digestive system in the lobster reconfiguring their brain networks depending on the behavioural context. This produces different types of behaviour. These were however single cell recordings, and it may not necessarily be the case that large scale brain networks behave in a similarly flexible way for cognitive processes. However, this perspective offers a way to address the question of putative mereological structure in the brain's large scale networks.

The transition problem deals with how quick and how often the brain can switch between different configuration of brain networks. In the supplementary

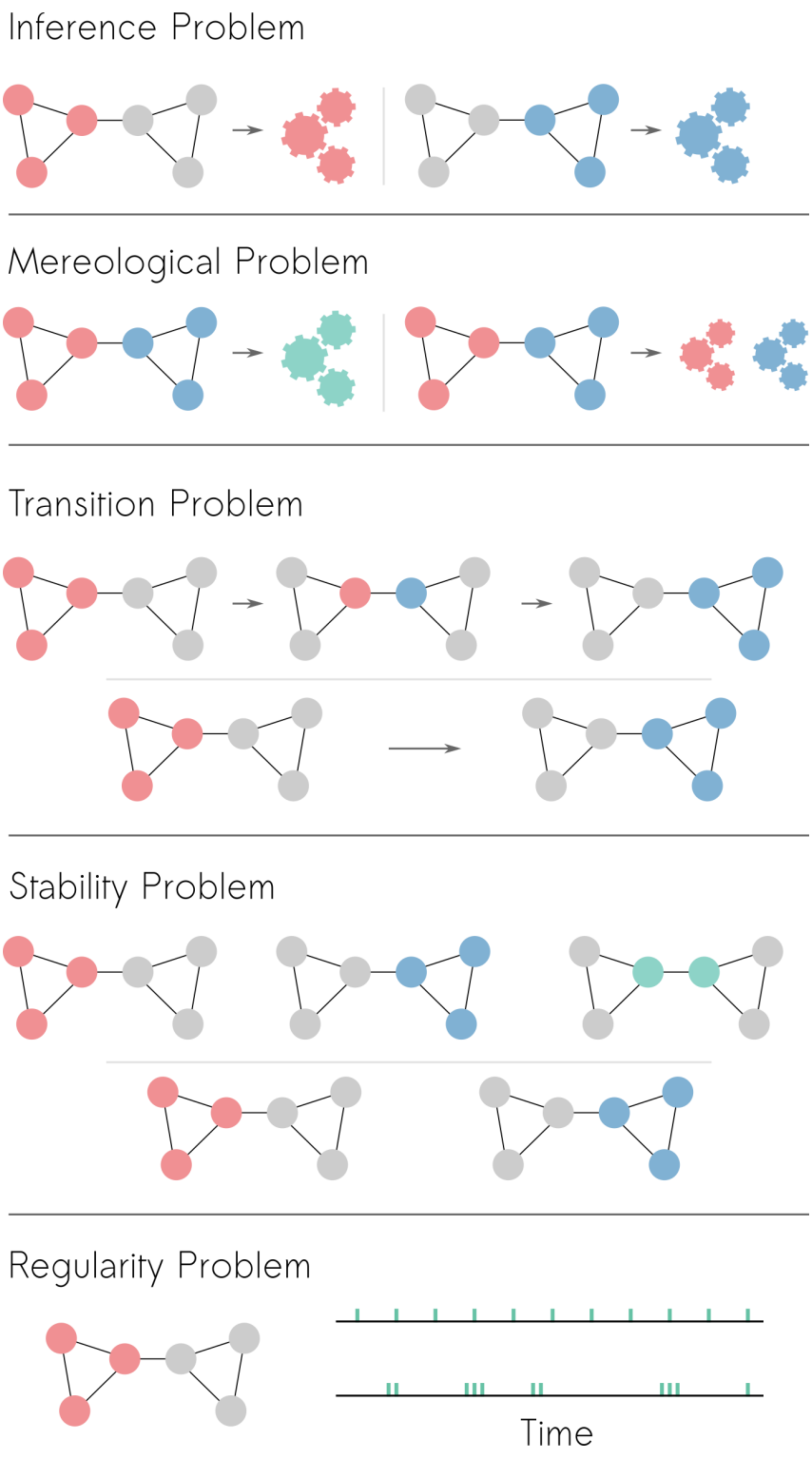

Figure 3.4: Illustration of several outstanding questions for temporal network theory to solve. 1. Inference Problems: how to go from a specific brain network activation to a biological mechanism. Mereological problem: given two brain networks each with an associated mechanism, does this create a new mechanism (left) or does this have an additive effect (right). Transition problem: do networks slowly transition from one to the other (top) or quickly (bottom). Stability problem: Are there multiple overlapping basis networks (top) or are all nodes assigned to one functional network (bottom). Regularity problem: how frequently do networks activate. This could be oscillatory (top right) or bursty (bottom right)

materials of *Paper III* we show that transitions between states appear to be gradual. However, Allan et al (258) showed that fMRI events occurs for only a brief period of time. Thus, researchers in functional neuroimaging still needs to account for the how quick and how often such transitions can occur. It is reasonable to assume that it takes more energy for the brain to constantly switch its functional brain network configuration and a fast and steady rate of brain network reconfiguration could possibly be taken to indicate mental fatigue (259).

Regarding the stability problem, despite the fact that multiple studies in flexibility of communities have been carried out, it is unclear if it is simply different large scales brain networks cooperating, or whether brain networks actually reconfigure. This is often hard to test. For example, Cole et al (187) found reconfiguration of hubs across different tasks, however, they presumed which brain networks the nodes belonged to *a priori*. Thus, this makes it difficult to know if it is brain network's changing their cooperation or if different brain networks temporarily emerge.

The stability problem can also be expressed in a slightly different way. When a certain brain network or network configuration is active, it is the case that additional configurations of periphery subnetworks are active that can effect or restrain behaviour. An example of this is the behavioural phenomena of bilingual participants changing their response to questions about morality depending on which language they were speaking (260–262). It is possible that this behaviour could be caused by a dynamic switch in brain network configuration that resulted in a difference in behaviour. There are a vast number of other psychological phenomena which can be discussed under the umbrella of the stability problem. The rigidity of brain network configurations under different circumstances still needs to be explored.

The regularity problem is partially addressed in this thesis in §3.3.2, *Paper III* and *Paper IV*. Here it is suggested that brain network states or configurations occurs in a bursty pattern. There is also evidence from EEG that switching between periods of high and low alpha (i.e. 10 Hz neural activity) occurs in

this temporal pattern as well (24,232,263). However, such work needs to be unified with oscillatory studies of the brain, where different ongoing dynamics have been assigned to different frequencies (264–267).

Here, we have mentioned a few of the properties regarding temporal network theory that are beginning to be explored and which of these properties that might be present the brain and revealed using temporal network theory applied to large-scale brain network functional neuroimaging data. Trying to seek answers to these questions will help us move towards the issue of how cognitive processes can be identified in the brain.

3.3.5 Summary of theme 2

The works in this thesis only managed to scratch the surface regarding implementing temporal network theory. The work in temporal network theory does raise a couple of unanswered questions which need to be solved:

1. Are the measures calculated capturing neural or non-neural activity (such as movement)?
2. Can they be used accurately in a task context?
3. How are the measures effected by different thresholding or scaling strategies?

If these outstanding questions can be answered, then temporal network theory can be applied to explore issues regarding complex cognitive processes.

3.4 Theme 3. Other multi-layer networks and networks regarding different time scales

While theme 1 and theme 2 consider applying functional connectivity across time, this is build on a number of assumptions. As stated in §2, a full descrip-

tion of the connection will require multilayer networks over time and frequency. In §1, it was stated that there are different time scales that the brain can be analysed on. Theme 3 investigated theses properties by testing different multi layer networks and studying different time scales. The papers within Theme 3 deals with (1) multi-layered network over frequency instead of time (*Paper V*); (2) investigating the severity from trauma on cognitive abilities later in time can be identified with functional connectivity (*Paper VI*).

3.4.1 Frequency differences in functional connectivity

In *Paper IV* temporal networks are defined in relation to a general multi-layered network. It is also detailed that a full connectome analysis will require more dimensions than just time in order to be a complete model. It is possible for networks to be expressed over other layers other than time. One such dimension we investigated was frequency. In *Paper V* a number of graphlets were expressed across frequency instead of time.

The traditional frequency bandwidth for resting-state studies in fMRI is approximately 0.01 to 0.1 Hz. It is known that this frequency band contains neural activity (268,269). Below this, there may be artefacts such as scanner drifts. Above this frequency range are physiological artefacts such as breathing. There are some indications that activity greater than 0.1 Hz may contain interesting information (270). Most studies still bandpass the fMRI signal within this classical frequency band of interest, containing oscillations with a duration between 10 and 100 seconds (i.e. considerable variance in these oscillations). The frequency bands of interest in many studies are called (Slow 2 (0.198–0.25 Hz), Slow 3 (0.073–0.198 Hz), Slow 4 (0.027–0.073 Hz) and Slow 5 (0.01–0.027 Hz)) (268). The motivation behind these frequency bands appears to arise from logarithmic cross-species idea property (271,272).

Different network properties across frequencies have been studied previously (59,171,269,273,274). Again, the above mentioned "slow" frequency bands were

often utilized to divide the signal into different components of interest. In paper *Paper V*, we were interested in resolving this at a fine-grain frequency resolution, which the Human Connectome Project's 0.72 TR allowed us to do. This allowed for 78 frequency bins across the frequency range of 0.01 and 0.1 Hz. We created a connectivity matrix at each frequency bin, i.e. frequency-graphlets, and explored multiple network properties across the frequency band. In *Paper V*, we found that a range of different measures from network theory (e.g. global efficiency and betweenness centrality) fluctuates over the traditional resting state fMRI frequency range.

The significance of this work is two fold. First, it illustrates that multi-layer networks have multiple additional dimensions that can be used in the model of the human connectome. Averaging over frequency may be loosing some interesting information, just like averaging over time. This shows that a more accurate network model with also contain frequency, even in fMRI. Second, it has implications for the sliding window method for dynamic connectivity which, depending on the length of the window, can become more sensitive to certain frequencies over others.

3.4.2 Traumatic brain injury

Clinical applications of functional connectivity are numerous (93,275). There have been many studies looking at connectivity estimates using fMRI for traumatic brain injury (TBI) (276). Most studies have investigated patients in the chronic phase of TBI.[7] Contrasting to healthy controls, alterations in brain connectivity have been identified in several brain networks: the default mode network (100,277), fronto-parietal network (100), salience network (278) and motor networks (279). More recently, investigations during the acute phase[8] in mild TBI have been reported (280). In TBI, a well studied biomarker is a neurotrophic protein S100B (281). Recent research have shown that high

[7]Chronic period includes the long term effects of the trauma (usually at least 6 months after the trauma occurred).

[8]The acute period is shortly after the trauma has occurred.

levels of S100B after trauma correlated with cognitive outcome, such as the GOS score (282,283).

Our cohort of 24 patients included patients in the early acute phase of mild and severe TBI (*Paper VI*). Our goal in this study was to investigate if functional brain connectivity correlated with the biomarker S100B, and thereby showing that this biomarker can be related to differences in brain connectivity. We found that differences in connectivity correlated with S100B levels in several brain areas which correspond to within- and between default mode, fronto-parietal, visual, auditory and motor brain networks. The significance of this is:

1. It helps justify the claim that biomarkers for trauma correlate to the ongoing functional activity of the brain.
2. There is some indication that the functional connectivity could be used to predict brain injury severity.

This attempt to show that there are changes in the network structure based on the levels of S100B illustrates that functional connectivity can correlate to a biomarker. It remains to be seen if functional connectivity can provide additional information in predicting cognitive outcome besides the information that is readily available in the neurotrauma unit. If the answer to this question is yes, it also becomes possible to use brain network information to detect which cognitive functions that are injured and the possibility opens to start appropriate rehabilitation at an earlier stage than usual. This would then be work considering functional connectivity on a longer time scale than the rest of this thesis. However, a larger patient population is needed to infer the effectiveness of functional connectivity in predicting the severity of TBI.

3.5 Theme 4: Tools for connectivity analysis.

The final theme of this thesis revolved around exploring the possibility of creating tools to assist network and temporal network analysis of brain activity.

This resulted in three separate tools. The first regards the creation of a network atlas, the second regards investigating temporal network theory, the third is about comparing dynamic functional connectivity methods.

3.5.1 Network atlas

Taking into account the theoretical importance networks are considered to have for cognition, there exist surprisingly few tools available to the researchers to accurately report which networks are involved. When writing the results section for *Paper VI*, we wanted to relate the brain activity clusters we had found to the underlying brain networks. Presently, there exists very few ways to this. There are multiple anatomical partitions that can be referred to (AAL (284), multi-modal atlas from the Human Connectome Project (285) and many others (161,286–289)). While other articles can be used as a reference point to define a brain network, researchers could call their network something new, or relate a certain brain region to a specific network. This leads to both an inflation of new names for brain networks and an increase in inaccuracy regarding which brain networks the given brain activity results actually relate to. Brain network names become based on both psychological and anatomical properties.

The first steps to make a network atlas tool for network classification was presented in *Paper VII*. Here, Neurosynth was used (290) to classify 144 brain network terms into 29 brain networks. These networks clustered into hierarchies with 6 different main branches. The significance of *Paper VII* is threefold:

1. Many cognitive functions overlap with their underlying brain networks. This again supports the idea of Model 4 over Model 3 in §1.2 as overlapping brain network regions are reused in different cognitive processes, configured slightly differently.

2. As many different network (e.g. "self network" and "social network") have considerable overlap, which emphasizes the need to unify network

terminology as, giving similar spatial brain activation patterns very different semantic names can cause misunderstandings.

3. It highlights the need for a tool for systematically reporting the results of brain activation studies in a context of brain networks.

In *Paper VII* we further published the templates for the 29 networks that clustered hierarchically along 6 main branches. Despite this significant degree of clustering of networks, we show that there is a considerable spatial overlap for all 6 top-level networks. The next step is to construct a network atlas which, for a given target contrast/activation image can be queried to give an approximation which network or networks that most strongly adhere to. Here follows an outline of some considerations that should taken when constructing a network-based brain atlas.

The goal is to have a tool that can be used to automically label networks. Such a tool will require two main components: (1) a set of network templates; (2) a method to compare some target image with the network templates.

The templates from *Paper VII* are useful for a preliminary network atlas, but they can be improved upon in a number of ways. First, the network templates are, in the present implementation, binary. This entails that classifying binary reference images will be easier than weighted (e.g. T-value masks). Second, the templates are hierarchical, this makes some measures for classifying a image less appropriate. Better templates can be improved in several ways, either by improving the methodology used in *Paper VII* or by deriving some other set of networks. Finally, multiple sets of network templates may be desirable. For example, if the atlas is going to be able to classify both voxel and surface space, different templates will be needed.

Regarding the method to compare a target brain activation image with the networks atlas, there are a number of possibilities. The Dice coefficient (i.e. the intersection divided by the union of the target image and template image) is one option. Another option is the to only consider the intersection, given the template image. A final option is to consider the intersection, given the target

image. These different strategies will have different consequences and can bias to smaller or larger templates. The optimal choice may depend on the type of templates used (so if one option is good for the templates in *Paper VII* it does not mean it is a good decision for all possible templates). The decision about which method to match the target image with the templates is also affected by whether it should also consider combinations of multiple networks from a set of templates or not. Considering every possible network combination would take far too much computational time. There are again multiple ways to deal with it. One possibility is to use a greedy approach where, at the first iteration, the best network is added too all masks in the next iteration (and so on). This continues until a optimal combination of combined network masks is found.

The automatic network labels (ANL)[9] classification is only in an early development stage (V0.0.1) and the work of this thesis was to create the templates and consider different naming strategies. An example of the classification in its current form is shown in *Figure 3.5*, which shows 10 of 20 automatically labelled ICA components. Here the 30 preprocessed subjects from the nilearn sample of the ADHD 200 dataset[10] were used. 20 ICA components were derived. These 20 ICA components are then compared against the template images from *Paper VII*. The names of each component is printed above. Here it can be seen that some of these brain networks are correct (e.g. the frontoparietal network), some are only identifying noise (e.g. the component marked occipitotemporal) and others where the classification seems to be suboptimal (e.g. the default mode network was split into a frontal and posterior components and the frontal part was classed as "emotion"). Thus while this software is not ready for automatically labelling networks, it can help assist identifying networks at the moment.

[9]The ANL code and templates can be found at https://github.com/wiheto/anl/ and the example (with all 20 components) is available at https://github.com/wiheto/anl/example/ica20/classify.ipynb

[10]http://fcon_1000.projects.nitrc.org/indi/adhd200/

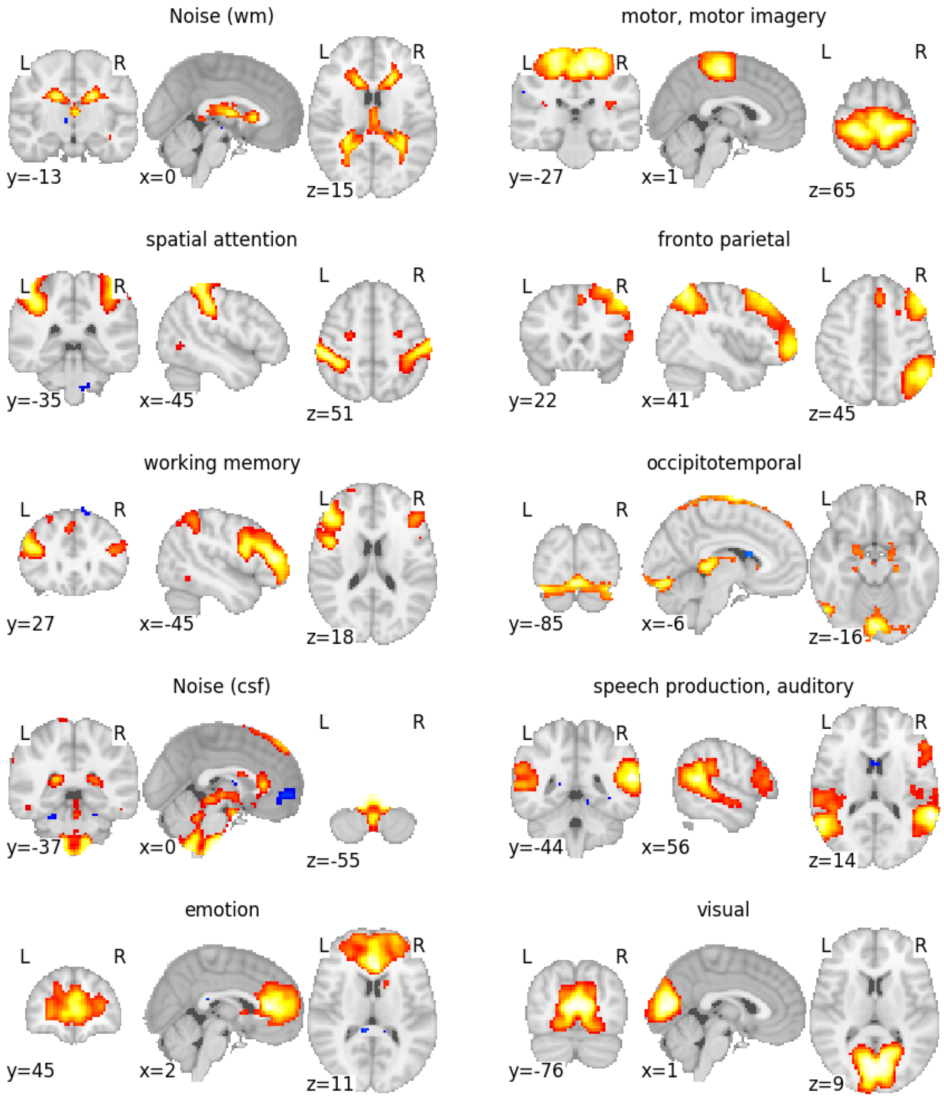

Figure 3.5: Example of ANLs classification with the 29 networks from *paper VII* and classifying networks based on the intersection given the template image. 10 ICA components are shown with an automatically assigned name. Some networks get an accurate name while others do not.

3.5.2 Temporal network tools (Teneto)

A lot of the work included in this thesis is dedicated to analyse how dynamic brain connectivity can be estimated so that temporal network theory can be implemented and used to test meaningful hypotheses regarding the brain's large-scale network dynamics. Creating accessible tools for other researchers to use is a natural step from the ideas and goals described in this thesis. Thus, while conducting the analysis for *Paper IV*, *Teneto* was created.[11] Teneto is a python package which can be used to derive, analyse, and plot temporal networks.

Teneto is based around three core modules:

teneto.derive: derives the connectivity estimates from time series data. The derivation steps that are included are the weighted Pearson methods (sliding window, tapered sliding window, spatial distance) and temporal derivatives. Post-processing steps (e.g. Box Cox transformation) can also be applied. HTML reports are generated for the derivation and post-processing steps to maximize reproducibility.

teneto.networkmeasures: quantifies networks properties. This list includes all those measures included in *Paper IV* and other measures are added over time.

teneto.plot: creates several different types of visualization tools. See *Figure 3.1* or *Paper IV* or *Paper VIII* for examples.

There are additional modules that deals with network simulations, and general utility functions for dealing with temporal network representations. There will also be an additional modules in the future for community detection and statistical inference of networks.

The aim is to create a easy to use software for people so that they can take preprocessed data and derive temporal networks, quantify network properties, generating reports, performing statistics on network measures, and use built-in facilities for plotting the results. Apart from providing this functionality,

[11] Available at https://github.com/wiheto/teneto. V0.2.1 is available at time of writing.

it entails striking a balance of automation on the one and hand, and user awareness of the all the steps carried out in the analysis pipeline through a "glassbox" on another hand. To create this user awareness, the reports generated by e.g. the derivation step are crucial. There are also plans to integrate it with the BIDs format (291). Regardless of all the features still to be implemented, the foundations are in place for researchers to derive dynamic functional connectivity and use temporal network theory on their functional neuroimaging data.

3.5.3 Comparing dynamic functional connectivity

In §2.3.3 and §3.2 it was stated that this thesis contains an evaluation of different dynamic functional connectivity methods. This evaluation is found in *Paper IX*. To compare and contrast different dynamic functional connectivity methods there needs to be some systematization regarding how this occurs. Preferably all methods are compared in the same battery of simulations. However, it is also hard for one person or group to implement every single dynamic functional connectivity method proposed, this means that most comparisons will only compare a handful of methods. In *Paper IX* we managed to find a compromise between systematization and accessibility of tools to compare the performance of dynamic functional connectivity methods.

We created *DFCBenchmarker*.[12] This contains a set of simulations and a set of methods which have been benchmarked. In the first version there are four simulations and five methods. However, DFCBenchmarker allows other researchers to test their own methodology against these methods. All a researcher needs to do is implement their method in Python. Then the same simulations and tests will be applied. This allows for comparing these new methods against the five methods tested in *Paper IX* and bundled with the first version of DFCBenchmarker. Researchers can then submit their results to us which will be collected and released as a report. The intention is to create reports based on the functions that researchers submit if the program is adopted. This will

[12] Available at https://github.com/wiheto/dfcbenchmarker

allow other researchers who wish to perform a dynamic functional connectivity analysis to clearly see which method appears to be the best for their purposes.

Chapter 4

Account for the openness of papers, data, and code in the thesis

In recent years issues regarding reproducibility of results has increased within science (292–296). Steps are being taken to improve the openness and reproducibility within the field (297,298). Three three pillars of open science have been described as the availability of the papers, data, and code (298). To this end, here follows an account of the availability of the data and code that were used in the papers in this thesis.

4.1 Availability of papers

All papers of the thesis that are currently published are under open access licences at their respective journals and available outline these. The unpublished ones will also be published under similar licences.

4.2 Data used

Much of the data used originated from open data repositories. This includes:

1. Nitrc[1] (*Paper I*, *Paper II*, *Paper IV*). Especially data from the Beijing eyes-open/eyes-closed dataset (256).
2. The Human Connectome Project[2] (*Paper III*, *paper V*).
3. Neurosynth[3] (*Paper VII*).

Paper VIII is a conceptual argument, although for a schematic representation also used data from Nitrc. *Paper IX* is a simulation paper where all data used is generated.

The patient data from *Paper VI* is currently not open. This information could be sensitive due to the heterogeneity of the group.[4] This is stored internally.

4.3 Code

Code for all the different projects can be found at https://github.com/wiheto/. Code always contains the key analysis code for all projects, but for some projects, the preprocessing steps are left out due to button pushes. All code is written in Matlab and/or Python.

Paper I: Main functions used in the analysis are available.[5] The code for this project was written in Matlab.

[1] https://nitrc.org
[2] https://humanconnectome.org
[3] https://neurosynth.org
[4] The heterogeneity is due to each person has different types of trauma, making anonymization via simply skull stripping difficult. There is also considerable amount of information that would be needed to supplement the images data, increasing the chances of identifying the patients.
[5] https://github.com/wiheto/phd_code/paper_i

Paper II: Main functions used in the analysis are available.[6] The code for this project was written in Matlab.

Paper III: Main functions used in the analysis are available.[7] The code for this project was written in Matlab.

Paper IV: The entire software package is available.[8] Further, the code used in the analysis is available.[9] The code for this project was written in Python.

Paper V: Main functions used in the analysis are available.[10] The code for this project was written in Matlab.

Paper VII: All code used in the analysis is available.[11] The code for this project was written in Matlab and Python.

Paper XI: The entire software package is available online.[12] The code for this project was written in Python.

The two exceptions here are *Paper VI* and *Paper VIII*. The latter, as stated above, was a conceptual argumentation which has no data or code that is part of the argument. *Paper VI* was the TBI study. It involved uses of SPM (235) and CONN (299) toolboxes. The structure of the analysis is saved with a .mat file but this is not publicly available. Like the raw data itself, this file contains information related to the patients (e.g. age, severity of trauma, different medications taken) and stored internally with the raw data.

[6] https://github.com/wiheto/phd_code/paper_ii
[7] https://github.com/wiheto/phd_code/paper_iii
[8] https://github.com/wiheto/teneto
[9] https://github.com/wiheto/phd_code/paper_iv
[10] https://github.com/wiheto/phd_code/paper_v
[11] https://github.com/wiheto/MMA_of_brain_networks
[12] https://github.com/wiheto/dfcbenchmarker

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Sammanfattning

Studier av hjärnans struktur och funktion i ett nätverksperspektiv har gett kunskap om både den friska och sjuka hjärnan. Kvantifiering av hjärnans nätverksaktivitet baseras vanligtvis på genomsnittet av aktiviteter över försök, frekvens eller tid och kallas för funktionell konnektivitet. Avhandlingens syfte är att utvidga analysen av hjärnans nätverk för att komma förbi dessa antagande och förenklingar. Funktionell konnektivitet som varierar över tid kallas oftast för dynamik funktionell konnektivitet. Denna avhandling överväger olika metoder att härleda en dynamisk funktionell konnektivitet representation av hjärnans aktivitet och därefter kvantifiera representationen med temporal nätverksteori.

Artikel I: diskuterar olika tolkningar av vad som anses "intressant" eller "hög" dynamisk funktionell konnektivitet. Valet av tolkning gör att olika kopplingar i hjärnan prioriterats.

Artikel II: diskuterar variansens stabilitet inom en tidsserie av dynamisk konnektivitet. Det här är ett viktigt preprocesseringssteg inom dynamisk funktionell konnektivitet som kan påverka senare analyser om det görs på ett inkorrekt sätt.

Artikel III: kvantifierar nivån av bristhet, det vill säga distributionen av temporala kopplingar, mellan olika kantmängder i fMRI data.

Artikel IV: ger en introduktion till och applicerar mått från temporal nätverksteori på fMRI data.

Artikel V: multi-nivå nätverksanalys av hjärnans nätverk under vila över olika frekvenser av BOLD responsen. Arbetet visar att en fullständig analys av hjärnans nätverk i fMRI kan även behöva specificera nätverk över olika frekvenser.

Artikel VI: undersöker om funktionell konnektivitet hos patienter med traumatisk hjärnskada korrelerar med variabler som är relaterad till kognitiv återhämtning efter trauma.

Artikel VII: är en massmeta-analys med Neurosynth som samlar olika nätverk från olika uppgifter till en hierarkisk nätverksstruktur. Detta arbete är början på en datadriven hierarkisk nätverksatlas över olika kognitiva fakulteter.

Artikel VIII: är en konceptuell översikt över olika antaganden om diverse populära metoder för att räkna ut dynamisk funktionell konnektivitet.

Artikel XI: utvärderar olika metoder för dynamisk funktionell konnektivitet. Studien är baserad på flera simulationer utformade för att spåra signalernas kovarians som fluktuerar över tid.

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